行政院國家科學委員會補助專題研究計畫成果報告

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※ I. 經由雙環[2.2.1]庚烯酮的光化學重排反應合成 ※
※ 環戊烷類天然物和前列腺素 ※
※ II. 3-氮代雙環[4.3.0]壬烷類生物鹼的合成 ※
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計畫類別：個別型計畫

計畫編號：NSC 90－2113－M－041－002－

執行期間：90 年 08 月 01 日至 91 年 07 月 31 日

計畫主持人：戴火木

共同主持人：

計畫參與人員：

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□赴國外出差或研習心得報告一份

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□國際合作研究計畫國外研究報告書一份

執行單位：嘉南藥理科技大學

中 華 民 國 91 年 10 月 23 日

行政院國家科學委員會專題研究計畫成果報告

I. 經由雙環[2.2.1]庚烯酮的光化學重排反應合成環戊烷類天然物和前列腺素
II. 3-氮代雙環[4.3.0]壬烷類生物鹼的合成

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計畫參與人員：曾景瑞（研究助理）

一、中文摘要

本研究報告分為二部分；第一部份為利用分子內自由基環合反應，建構 indolizidine 骨架，合成 dendroprimine。第二部份為利用雙環[2.2.1]庚烯酮的光化學重排反應為關鍵步驟合成環戊烷類天然物和前列腺素

關鍵詞：分子內自由基環合反應；環戊烷類天然物；前列腺素；indolizidine；dendroprimine。

Abstract

Sodium borohydride regioselectively reduced various 3-sulfonyl glutarimides **1** to hydroxy piperidones **2**, which were further dehydrated to 3,4-dihydro-5-sulfonylpyridin -2-ones **3** in the presence of boron trifluoride. Formal synthesis of 8a-*epi*-dendroprimine (**4**) possessing an indolizidine ring system has been accomplished *via* intramolecular radical cyclization of cyclic vinyl sulfone **5**.

The synthesis of cyclopentanoid natural products, iridoid monoterpenes and prostaglandins, was achieved from a common intermediate **2**, which was obtained from **1** via photochemical rearrangement.

Keywords: intramolecular radical cyclization; cyclopentanoid natural products; indolizidine; prostaglandins; dendroprimine.

JOC*Note*

Regioselective Reduction of 3-Sulfonyl Glutarimides to 3,4-Dihydro-5-sulfonylpyridin-2-ones. Formal Synthesis of the Indolizidine 8a-*epi*-Dendroprimine

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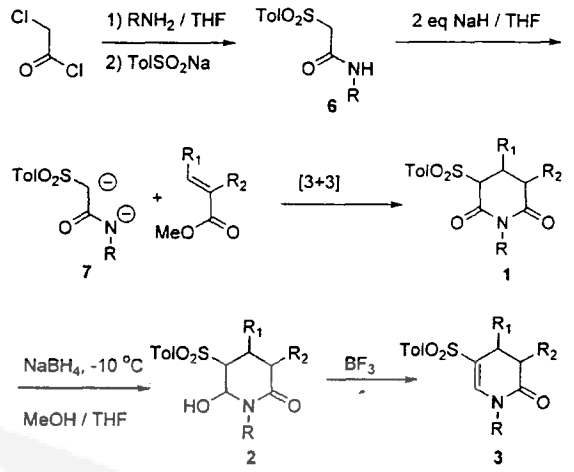
Received January 20, 2002

Abstract: Sodium borohydride regioselectively reduced various 3-sulfonyl glutarimides **1** to hydroxy piperidones **2**, which were further dehydrated to 3,4-dihydro-5-sulfonylpyridin-2-ones **3** in the presence of boron trifluoride. Formal synthesis of 8a-*epi*-dendroprimine (**4**) possessing an indolizidine ring system has been accomplished via intramolecular radical cyclization of cyclic vinyl sulfone **5**.

Regioselective reduction of cyclic imides has attracted considerable interest among organic chemists,[1-4] partly because the resulting hydroxylactams can be converted to corresponding *N*-acyliminium intermediates and then further transformed into different alkaloids, such as indolizidines, quinolizidines, isoquinolines, and indoles.[5] In cases of reduction of nonsymmetrically substituted cyclic imides, it was reported that glutarimides seem to be preferentially reduced at the less hindered carbonyl group.[3,4] In this report, we describe a general method which regioselectively reduces the carbonyl group on 3-sulfonyl glutarimides **1** and leads to corresponding hydroxylactams **2**, which are then further converted to 3,4-dihydro-5-sulfonylpyridin-2-ones **3**. Formal synthesis of 8a-*epi*-dendroprimine (**4**) via intramolecular radical cyclization of cyclic vinyl sulfone **5** is also reported.

SCHEME 1



Previously, we reported an efficient synthesis of 4- or 5-substituted 3-sulfonyl glutarimides **1** via a stepwise [3 + 3] cycloaddition.[6] Sequential treatment of chloroacetyl chloride with primary amines and sodium *p*-toluenesulfinate furnished α-toluenesulfonyl acetamide **6** in 90% yield. After the reaction of **6** with 2 equiv of sodium hydride, the resulting dianion **7** reacted with a variety of α,β-unsaturated esters to afford the corresponding substituted 3-toluenesulfonyl glutarimides **1**. The *trans* stereochemistry of **1b** was established by X-ray analysis. The stereochemistries of all the other cycloadducts of **1** were compared by their ^{1}H NMR spectra with that of **1b** (a ^{1}H HNR singlet at δ 3.87 was assigned to an equatorial proton on the C_3 carbon in the boat form conformation of **1b**).[6] In the course of our application of **1** in alkaloid synthesis, we found that treatment of **1** with excess sodium borohydride in methanol−tetrahydrofuran (1:2) at −10 °C furnished **2** exclusively. The presence of the strong electron-withdrawing sulfonyl group at the C_3 position increased the electrophilicity of C_2, which may account for the regiochemistry of reduction. To confirm these results, hydroxylactams **2** were treated with boron trifluoride in the presence of anhydrous magnesium sulfate, and the corresponding dehydration products **3** were obtained in moderate to good yields (Scheme 1). Several examples were examined, and the results are listed in Table 1.

For the synthesis of 8a-*epi*-dendroprimine (**4**) shown in Scheme 2,[7] glutarimide **8** was prepared in quantitative yield by treatment of **1b** with aluminum trichloride in refluxing benzene. Compound **8** was converted to chloride **1j**, which, upon treatment with excess sodium borohydride in MeOH−THF solution at −10 °C, furnished hydroxy lactam **2j**.[8] Without purification, subsequent

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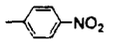
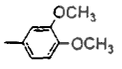
(1) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **2000**, *41*, 1993.
(2) Ducrot, P.; Thal, C. *Tetrahedron Lett.* **1999**, *40*, 9037.
(3) Tagmann, E.; Sury, E.; Hoffmann, K. *Helv. Chim. Acta* **1954**, *37*, 185.
(4) Watanabe, T.; Hamaguchi, F.; Ohki, S. *Yakugaku Zasshi* **1973**, *93*, 845; *Chem. Abstr.* **1973**, *79*, 78328.
(5) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Roth, E.; Altman, J.; Kapon, M.; Ben-Ishai, D. *Tetrahedron* **1995**, *51*, 801. (c) Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *Tetrahedron Lett.* **1996**, *37*, 7841. (d) Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210. (e) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144. (f) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J. C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361. (g) Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; McMills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914. (h) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J. C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661. (i) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169.
(6) Chang, M.-Y.; Chang, B.-R.; Tai, H.-M.; Chang, N.-C. *Tetrahedron Lett.* **2000**, *41*, 10273.
(7) (a) Diederich, M.; Nubbemeyer, U. *Synthesis* **1999**, 286. (b) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998.
(8) Hubert, J. C.; Wunberg, T. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

10.1021/jo025539p CCC: $22.00
Published on Web 06/13/2002

TABLE 1. Synthesis of 3 via Regioselective $NaBH_4$ Reduction of 1[a,b]

entry	R_1	R_2	R	yield of 3
a	−H	−H	−Bn	45%
b	$-CH_3$	−H	−Bn	91%
c	−H	$-CH_3$	−Bn	68%
d		−H	−Bn	73%
e		−H	−Bn	55%
f		−H	−PMB	80%
g		−H	−PMB	69%
h		−H	−PMB	75%
i	$-CH_3$	−H		95%
j	$-CH_3$	−H	$-(CH_2)_3Cl$	97%

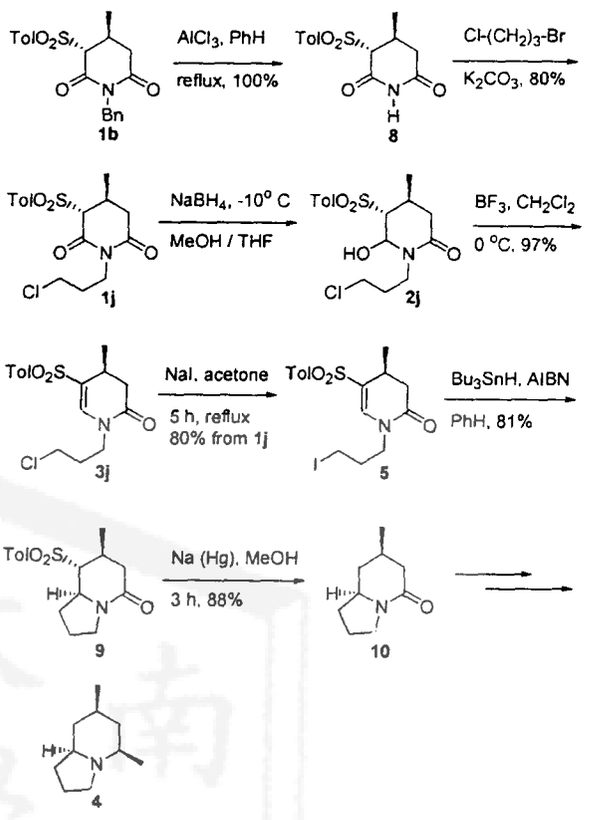
[a] All yields were based on glutarimides **1**. [b] The structures of **1b** and **3g** were confirmed by X-ray analysis.

boron trifloride dehydration of **2j** provided vinyl sulfone **3j** from **1j** in 97% yield.

For the synthesis of an indolizidine skeleton, chloride **3j** was first converted to the corresponding iodide **5** with sodium iodide. Intramolecular radical cyclization of **5** with tributyltin hydride in the presence of AIBN gave indolizidine **9** (81%) as a single diastereomer. To the best of our knowledge, this is the first example of the radical cyclization of cyclic vinyl sulfone to build up an indolizidine carbon skeleton. Reductive desulfonation of **9** with sodium amalgam gave **10** as a single diastereomer in 88% yield.[9] The strucure of **10** was confirmed by comparison of the ^1H and ^{13}C NMR spectra with those of an authentic sample provided by Professor Udo Nubbemeyer.[7a] The diastereoselective production of **9** can be explained by the formation of the more stable intermediate **11a** instead of **11b** in the ring formation step. This rationalization was supported by X-ray crystallography of compound **3g** (Figure 1), prepared in our laboratory. In compound **3g**, the substituents at C_4 and the nitrogen atom are *cis* to each other. Since compound **10** has been transformed into 8a-*epi*-dendroprimine (**4**), this work constitutes a formal total synthesis of racemic 8a-*epi*-dendroprimine (**4**).[7a]

In summary, we successfully performed the regioselective reaction of 3-sulfonyl glutarimides **1**, leading to 3,4-dihydro-5-tosylpyridin-2-ones **3** in moderate to excellent yields and intramolecular radical cyclization of cyclic vinyl sulfone **5** to construct indolizidine carbon skeleton **10**. This methodology has proved applicable for the synthesis of the indolizidine alkaloid 8a-*epi*-dendroprimine (**4**). Further syntheses of piperidine, indolizidine, quinolizidine, and indole alkaloids are currently underway in our laboratory.

SCHEME 2



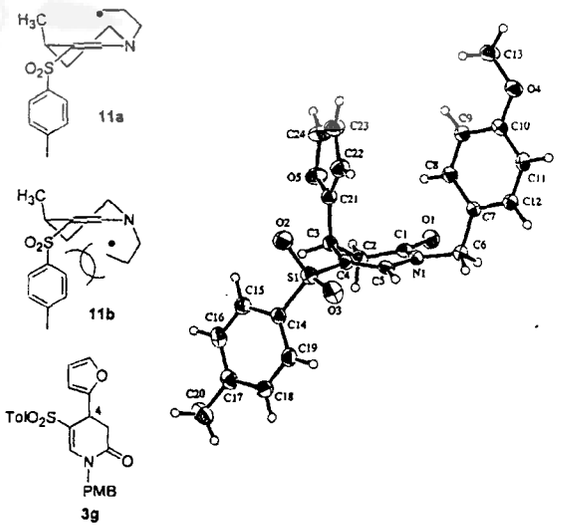


FIGURE 1. Intermediates of **11** and X-ray crystallography of **3g**.

(9) Satoh, T.; Oguro, K.; Shishikura, J.; Kanetaka, N.; Okada, R.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2339.

Experimental Section

Before use, THF and benzene were distilled from a deep blue solution resulting from sodium and benzophenone under nitrogen. All reagents and solvents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) analysis was performed with precoated silica gel (60 f_{254} plates), and column chromatography was carried out on silica (70−230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars.

General Procedure to *N*-Substituted 2-(Toluene-4-sulfonyl)acetamide (6). A mixture of *N*-substituted 2-chloroacetamide (68.5 mmol) and toluene-4-sulfonate sodium salt (1.7 g, 75.4 mmol) in dioxane (30 mL) and water (30 mL) was refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was recrystallized from ethyl acetate to give **6**.

***N*-Benzyl-2-(toluene-4-sulfonyl)acetamide:** 74% yield; IR ($CHCl_3$, cm^{-1}) 3354, 1665; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.37−7.25 (m, 7H), 7.08 (br s, 1H), 4.44 (d, J = 5.5 Hz, 2H), 4.02 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 160.5 (s), 145.6 (s), 137.2 (s), 134.9 (s), 130.1 (d, 2C), 128.8 (d, 2C), 128.1 (d, 2C), 128.0 (d, 2C), 127.7 (d), 61.9 (t), 44.0 (d). Mass *m/z* (EI, 70 eV): 303 (M^+, 1%), 148 (100%). HRMS calcd for $C_{16}H_{17}NO_3S$ (M^+): 303.0929. Found: 303.0935. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.02; H, 5.31; N, 4.56.

General Procedure of [3 + 3] Cycloaddition to Glutarimides 1. To a suspension of sodium hydride (2.00 g, 60% dispersion in oil, washed three times with dry hexane) in dry THF (100 mL) was added 2-sulfonylacetamide (**1**) (20 mmol) in portions. After 20 min, α,β-unsaturated esters (20 mmol) in THF (30 mL) were added to the suspension mixture over a period of 30 min. The mixture was stirred for 12 h at room temperature. The reaction was quenched with aqueous sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate) to give glutarimides **1**.

(3*R,4*S**)-1-Benzyl-4-methyl-3-(toluene-4-sulfonyl)-3,4-dihydro-5*H*-pyridine-2,6-dione (1b):** 95% yield; mp 202−203 °C; IR ($CHCl_3$, cm^{-1}) 1675; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 2H), 7.36−7.24 (m, 7H), 5.09 (d, J = 14.0 Hz, 1H), 4.88 (d, J = 14.0 Hz, 1H), 3.87 (s, 1H), 3.51 (dd, J = 6.0, 18.0 Hz, 1H), 3.21−3.15 (m, 1H), 2.60 (d, J = 18.0 Hz, 1H), 2.43 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (s), 164.2 (s), 145.6 (s), 136.4 (s), 134.3 (s), 129.7 (d, 2C), 128.8 (d, 2C), 128.6 (d, 2C), 128.3 (d, 2C), 127.4 (d), 71.7 (d), 117.5 (s), 43.2 (t), 36.0 (t), 23.9 (d), 21.7 (q), 20.3 (q). Mass *m/z* (EI, 70 eV): 371 (M^+, 1%), 91 (100%). HRMS calcd for $C_{20}H_{21}NO_4S$ (M^+): 371.1191. Found: 371.1187. Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.20; H, 5.92; N, 3.80.

General Procedure of Regioselective Reduction of Glutarimides 1 to 3,4-Dihydro-5-sulfonylpyridin-2-ones 3. A suspension of sodium borohydride (106 mg, 2.8 mmol) and glutarimides **1** (1.5 mmol) in THF (30 mL) and methanol (15 mL) was stirred for 2 h at −10 °C. After saturated aqueous sodium bicarbonate was added to destroy the excess reduction agent at this temperature, organic solvents were removed under reduced pressure. The residue was extracted with dichloromethane, and the combined organic extracts were washed with brine, dried, filtered, and concentrated to afford **2**. Without further purification, boron trifloride diethyl etherate (0.5 mL) was added to a solution of the residue and anhydrous magnesium sulfate (50 mg) in dichloromethane (20 mL) at 0 °C and stirred at this temperature for 30 min. The reaction mixture was quenched with saturated aqueous sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 2:1) to give 3,4-dihydro-5-sulfonylpyridin-2-ones **3**.

(4*S,5*R**)-1-Benzyl-6-hydroxy-5-(toluene-4-sulfonyl)-4-phenyl-2-piperidinone (2d):** IR ($CDCl_3$, cm^{-1}) 3365, 1653; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 7.11−7.02 (m, 5H), 6.96−6.91 (m, 4H), 5.68 (s, 1H), 5.12 (d, J = 14.5 Hz, 1H), 4.40 (d, J = 14.5 Hz, 1H), 4.13 (br s, 1H), 4.01−3.95 (m, 1H), 3.68 (dd, J = 2.5, 11.5 Hz, 1H), 3.00 (dd, J = 7.5, 18.0 Hz, 1H), 2.52 (dd, J = 9.5, 18.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2 (s), 144.2 (s), 139.4 (s), 136.9 (s), 136.3 (s), 129.3 (d, 2C), 128.8 (d, 2C), 128.5 (d, 4C), 128.1 (d, 2C), 127.9 (d, 2C), 127.8 (d), 127.2 (d), 77.5 (d), 68.5 (d), 48.3 (t), 40.0 (t), 35.8 (d), 21.5 (q). Mass *m/z* (EI, 30 eV): 435 (M^+, 15.7%), 91 (100%).

1-(3-Chloropropyl)-4-methyl-5-(toluene-4-sulfonyl)-3,4-dihydropyridin-2-one (3j): 97% yield; IR ($CDCl_3$, cm^{-1}) 1692, 1644; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.35 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 3.89 (td, J = 6.5, 13.5 Hz, 1H), 3.65−3.50 (m, 1H), 2.77−2.71 (m, 1H), 2.57 (dd, J = 7.0, 16.0 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, J = 2.0, 16.0 Hz, 1H), 2.10 (quintet, J = 7.0 Hz, 2H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 168.3 (s), 144.3 (s), 138.0 (s), 137.6 (s), 129.9 (d, 2C), 127.6 (d, 2C), 122.8 (s), 45.2 (t), 41.6 (t), 38.7 (t), 31.2 (t), 26.6 (d), 21.6 (q), 18.5 (q). Mass (EI, 70 eV): 343 (M^+, Cl = 37, 18%), 341 (M^+, Cl = 35, 49%), 91 (100%). HRMS calcd for $C_{16}H_{20}ClNO_3S$ (M^+): 341.0852. Found: 341.0848. Anal. Calcd for $C_{16}H_{20}ClNO_3S$: C, 56.21; H, 5.90; N, 4.10. Found: C, 56.30; H, 5.98; N, 3.91.

(3*R,4*S**)-4-Methyl-3-(toluene-4-sulfonyl)piperidine-2,6-dione (8).** A suspension of **1b** (2.00 g, 5.4 mol) and aluminum chloride (3.60 g, 27.0 mmol) in benzene (30 mL) was refluxed for 8 h under nitrogen. After removal of the solvent, water was added to the residue, which was then extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was recrystallized from ethyl acetate to give compound **8** (1.50 g, quantitative). Mp 172−173 °C; IR ($CDCl_3$, cm^{-1}) 3360, 1711; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 3.82 (s, 1H), 3.40 (dd, J = 5.5, 18.0 Hz, 1H), 3.30−3.24 (m, 1H), 2.52 (d, J = 18.0 Hz, 1H), 2.48 (s, 3H), 1.21 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 170.3 (s), 164.1 (s), 146.1 (s), 134.6 (s), 130.0 (d, 2C), 129.0 (d, 2C), 71.0 (d), 35.3 (t), 25.2 (d), 21.8 (q), 20.3 (q). Mass (EI, 70 eV): 282 (M^+, 1%), 91 (100%). HRMS calcd for $C_{13}H_{15}NO_4S$ (M^+): 281.0722. Found: 281.0725. Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.41; H, 5.51; N, 4.63.

(3*R,4*S**)-1-(3-Chloropropyl)-4-methyl-3-(toluene-4-sulfonyl)-3,4-dihydro-5*H*-pyridine-2,6-dione (1j).** A solution of **8** (300 mg, 0.10 mol), potassium carbonate (0.5 g), and 1-bromo-3-chloropropane (400 mg, 2.3 mmol) in acetone (15 mL) was stirred at room temperature for 10 h. After removal of the solvent, the residue was added to saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was recrystallized from dichloromethane to afford compound **1j** (300 mg, 80%). Mp 133−134 °C; IR ($CDCl_3$, cm^{-1}) 1677; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 3.96 (dt, J = 2.5, 7.0 Hz, 2H), 3.91 (s, 1H), 3.55 (t, J = 7.0 Hz, 2H), 3.44 (dd, J = 6.0, 18.0 Hz, 1H), 3.21−3.14 (m, 1H), 2.59 (d, J = 18.0 Hz, 1H), 2.48 (s, 3H), 2.03 (quintet, J = 7.0 Hz, 2H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 170.2 (s), 164.5 (s), 146.1 (s), 134.8 (s), 130.0 (d, 2C), 128.8 (d, 2C), 71.8 (d), 42.0 (t), 37.9 (t), 36.0 (t), 30.8 (t), 24.0 (d), 21.8 (q), 20.3 (q). Mass (EI, 70 eV): 360 (M^+ + 1, Cl = 37, 0.6%), 358 (M^+ + 1, Cl = 37, 1.6%), 91 (100%). Anal. Calcd for $C_{16}H_{20}ClNO_4S$: C, 53.70; H, 5.63; N, 3.91. Found: C, 53.38; H, 5.78; N, 3.85.

1-(3-Iodopropyl)-4-methyl-5-(toluene-4-sulfonyl)-3,4-dihydropyridin-2-one (5). A solution of **3j** (1.00 g, 2.90 mol) and sodium iodide (0.40 g, 8.0 mmol) in acetone (20 mL) was refluxed for 5 h. After removal of the solvent, water was added to the residue, which was then extracted with dichloromethane. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographed on silica

(hexane/ethyl acetate 1:1) to furnish compound **5** (1.00 g, 80%): IR ($CDCl_3$, cm^{-1}) 1691, 1644; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.36 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 3.83 (td, J = 7.0, 13.5 Hz, 1H), 3.53 (td, J = 7.0, 13.5 Hz, 1H), 3.18–3.08 (m, 2H), 2.77–2.71 (m, 1H), 2.57 (dd, J = 7.0, 16.0 Hz, 1H), 2.45 (s, 3H), 2.38 (dd, J = 2.0, 16.0 Hz, 1H), 2.15 (quintet, J = 7.5 Hz, 2H), 0.96 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 168.3 (s), 144.3 (s), 137.9 (s), 137.6 (s), 130.0 (d, 2C), 127.7 (d, 2C), 122.9 (s), 48.1 (t), 38.7 (t), 32.1 (t), 26.6 (d), 21.6 (q), 18.6 (q), 1.3 (t). Mass (EI, 70 eV): 433 (M^+, 18%), 91 (100%). HRMS calcd for $C_{16}H_{20}INO_3S$ (M^+): 433.0209. Found: 433.0206. Anal. Calcd for $C_{16}H_{20}INO_3S$: C, 44.35; H, 4.65; I, 29.29; N, 3.23; O, 11.08; S, 7.40. Found: C, 44.21; H, 4.71; N, 3.05.

(7*S,8*R**,8a*S**)-7-Methyl-8-(toluene-4-sulfonyl)hexahydro-6*H*-indolizin-5-one (9).** To a solution of **5** (300 mg, 0.70 mol) and AIBN (9.5 mg) in benzene (30 mL) was added tributyltin hydride (250 mg) in benzene (30 mL) via syringe pump over a period of 2 h under nitrogen at refluxing temperature. The mixture was refluxed for 4 h. After the addition of water, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographed on silica (hexane/ethyl acetate 1:1) to provide compound **9** (200 mg, 81%): IR ($CDCl_3$, cm^{-1}) 1655; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.41 (s, 1H), 3.88 (dt, J = 6.5, 9.0 Hz, 1H), 3.63–3.58 (m, 1H), 3.40–3.34 (m, 1H), 2.82 (dd, J = 3.0, 9.0 Hz, 1H), 2.73–2.65 (m, 1H), 2.51–2.46 (m, 1H), 2.48 (s, 3H), 2.35–2.28 (m, 1H), 2.15 (dd, J = 2.0, 15.0 Hz, 1H), 1.96–1.89 (m, 1H), 1.83–1.67 (m, 2H), 0.89 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 169.3 (s), 145.5 (s), 134.6 (s), 130.2 (d, 2C), 128.8 (d, 2C), 71.5 (d), 55.3 (d), 44.1 (t), 38.1 (t), 34.8 (t), 29.0 (d), 23.4 (t), 22.6 (q), 21.7 (q). Mass (EI, 70 eV): 308 (M^+, 5%), 136 (100%). HRMS calcd for $C_{16}H_{21}NO_3S$ (M^+): 307.1242. Found: 307.1237.

(7*R,8a*S**)-7-Methylhexahydroindolizin-5-one (10).** A solution of **9** (200 mg, 0.60 mol), disodium hydrogen phosphate (60 mg), and sodium amalgam (2.0 g, 6%) in methanol (10 mL) was stirred at room temperature under nitrogen for 3 h. The mercury was removed, and the solvent was stripped off under reduced pressure. Water was added to the residue, which was then extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographed on silica (hexane/ethyl acetate 1:1) to afford compound **10** (88 mg, 88%): IR ($CDCl_3$, cm^{-1}) 1625; ^1H NMR (500 MHz, $CDCl_3$) δ 3.62–3.55 (m, 1H), 3.46–3.39 (m, 2H), 2.51 (dd, J = 3.0, 16.0 Hz, 1H), 2.10–2.02 (m, 2H), 1.99–1.86 (m, 3H), 1.81–1.77 (m, 1H), 1.41 (dq, J = 7.0, 11.5 Hz, 1H), 1.07–0.98 (m, 4H), 1.02 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 M Hz, $CDCl_3$) δ 169.0 (s), 59.0 (d), 44.6 (t), 39.7 (t), 37.6 (t), 33.3 (t), 28.5 (d), 22.2 (t), 21.6 (q). Mass (EI, 70 eV): 153 (M^+, 65%), 83 (100%). HRMS calcd for $C_9H_{15}NO$ (M^+): 153.1154. Found: 153.1157.

Acknowledgment. Financial support from the National Science Council of the Republic of China is gratefully acknowledged. The authors would also like to thank Professor Michael Yen-Nan Chiang (National Sun Yat-Sen University) for X-ray analysis and Professor Udo Nubbemeyer (Freie University) for sending spectra data of compound **10** to us for comparison.

Supporting Information Available: Characterization data for compounds **1d–h** and **3a–i**. This information is available free of charge via the Internet at http://pubs.acs.org.

JO025539P

Synthesis of Iridoid Monoterpenes and Prostaglandins, *via* Photochemical Rearrangement of Bicyclo[2.2.1]hept-5-en-2-one

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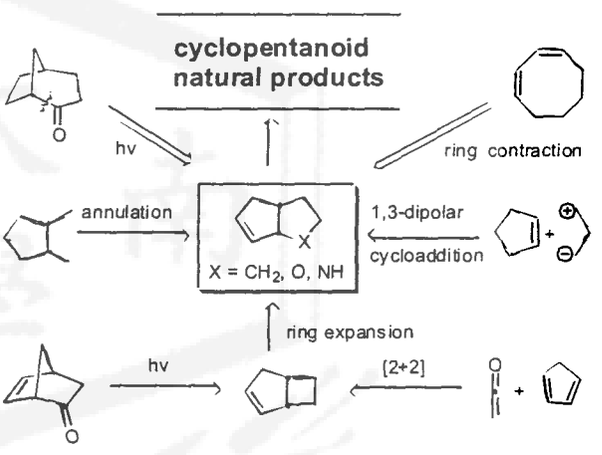
The synthesis of cyclopentanoid natural products, iridoid monoterpenes and prostaglandins, was achieved from a common intermediate **2**, which was obtained from **1** *via* photochemical rearrangement.

INTRODUCTION

Cyclopentanoid natural products have proliferated in the last four decades. Several of these families, such as iridoid monoterpenes,[1] diquinanes,[2] and triquinanes[3] have received the attention of synthetic chemists due to the complexicity of the structure and their biological activities. This has stimulated interest in preparing such substances and to meet the methodological challenges of constructing cyclopentanoid skeletons.[4]

A number of strategies have been developed in the building up of the *cis*-bicyclo[3.3.0]octene skeleton (Scheme I), which is one of the most important precursors in the synthesis of cyclopentanoid natural products.[5] Among the numerous methods of constructing *cis*-bicyclo[3.3.0]octene, ring expansion of *cis*-bicyclo[3.2.0]heptenones is not only an effective procedure to *cis*-bicyclo[3.3.0]octenes but also to 1-oxo- or 1-aza-bicyclo[3.3.0]octenes.[6] However, the [2+2] cycloaddition of cyclopentadiene and ketene approach to the construction of bicyclo[3.2.0]heptenone has been restricted by the functionalization of the cycloadducts.[7] Photochemical behavior of β,γ-unsaturated ketones has been well studied.[8] Nevertheless, only a few examples of photochemical rearrangement of bicyclo[2.2.1]heptenones have been reported, most of them concentrated in mechanistic studies. In this paper, we report photochemical rearrangement of bicyclo-[2.2.1]hept-5-en-2-one **1** to *cis*-bicyclo[3.2.0]hept-2-en-7-one **2**, as the key step in the synthesis of iridoids and prostaglandins.

Scheme I

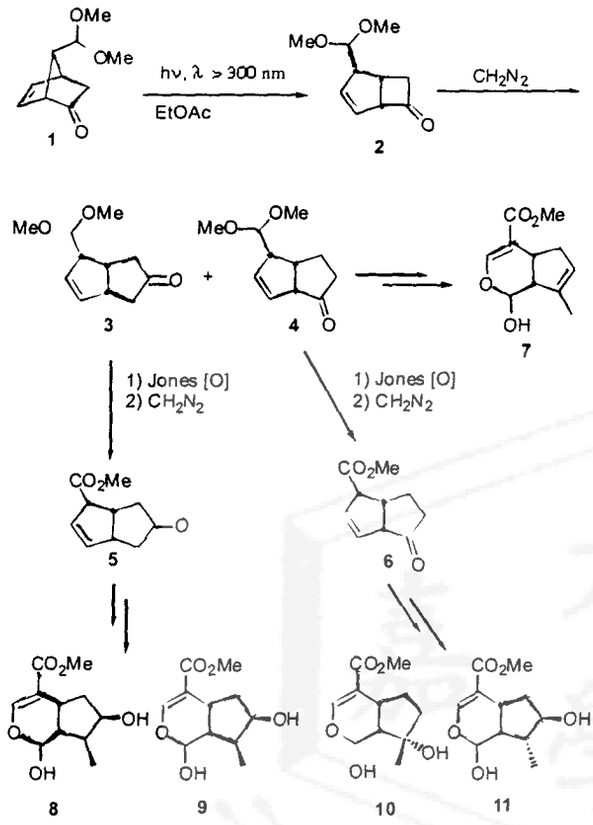


RESULTS AND DISCUSSION

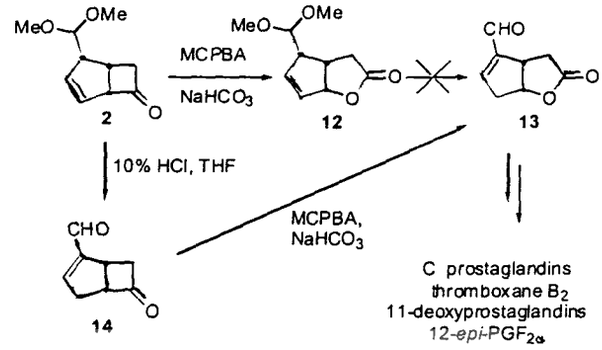
The readily available bicyclo[2.2.1]heptenone **1** was chosen as the starting material.[9] Irradiation of **1** in cyclohexane in Rayonet reactor ($\lambda > 300$ nm) afforded the 1,3-acyl shift product bicyclo[3.2.0]heptenone **2** in 78% yield. Subsequent ring enlargement of **2** with diazomethane gave a mixture of cyclopentanone **3** and regioisomer **4** in 1.5:1 ratio. Both diquinanes **3** and **4** were useful in the synthesis of iridoids. The ^{1}H and ^{13}C NMR data of **4** were identical with those of an authentic sample previously produced in our laboratory.[10] Since compound **4** has been transformed into 10-deoxygeniposide (**7**), this work constitutes a formal total synthesis of 10-deoxygeniposide (**7**).[10]

With treatment of **3** with Jones reagent followed by methylation of the resulting acid with diazomethane, acetal **3** was converted to ester **5**. The ^{1}H and ^{13}C NMR spectra of **5** were identical with those of an authentic sample previously produced in our laboratory.[11] Since compound **5** had been already transformed to loganin (**8**) and hydroxyloganin (**9**), this work constitutes a formal total synthesis of loganin (**8**) and hydroxyloganin (**9**).[11]

Scheme II



Scheme III



Treatment of **4** with Jones reagent followed by esterification of the resulting acid with diazomethane furnished ketoester **6**. The ^1H and ^{13}C NMR spectra of **6** were identical with those of an authentic sample previously produced in our laboratory.[12] Since compound **6** had been already transformed to mussaenoside (**10**) and 8-epiloganin (**11**), this work constitutes a formal total synthesis of mussaenoside (**10**) and 8-epiloganin (**11**).[12]

The route to the synthesis of prostaglandins is shown in Scheme III. Baeyer-Villiger oxidation of **2** with MCPBA in basic condition provided lactone **12** in 93% yield. Further treatment of the acetal **12** with various aqueous acid solutions resulted in complex mixtures.[13] After great effort, the synthesis of **13** was achieved as follows: Hydrolysis of **2** with hydrochloride in aqueous THF solution afforded aldehyde **14**, which was subsequently reacted with MCPBA to yield the Baeyer-Villiger oxidation product **13**. The structure of **13** was confirmed by comparison of the ^1H NMR spectra with an authentic sample provided by Renaud.[14] Since compound **13** has been previously converted to prostaglandins[15] and thromboxane B_2,[16] this procedure constitutes a new approach to the synthesis of racemic prostaglandins.

In summary, the successful synthesis of iridoids and prostaglandins demonstrate the utility of the photochemical rearrangement of bicyclo[2.2.1]hept-5-en-2-one **1** as a key step in the synthesis of cyclopentanoid natural products. Efforts toward the synthesis of other natural products are currently underway in our laboratory.

EXPERIMENTAL

General

THF was distilled before use from a deep blue solution resulting from sodium and benzophenone under nitrogen. All reagents and solvents were obtained from commercial sources and used without further purification. Thin layer chromatography (TLC) analysis was performed with precoated silica gel (60 f_{254} plates) and column chromatography was carried out on silica (70~230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-2000 spectrometer. ^1H HNR spectra were determined at 300 MHz, and ^{13}C NMR spectra were determined at 75 MHz on a Varian VXR 300 spectrometer in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS (tetramethylsilane) in the solvents specified. The multiplicities of ^{13}C signals were determined by DEPT techniques. Mass spectra (MS) were measured on a VGQUATTRO 5022 mass spectrometer. High resolution mass (HRMS) values were obtained on a JEOL JMSHY 110 mass spectrometer. El-

elemental analyses (EA) were performed on a Heraeus CHN-O analyzer.

(1*R,4*S**,5*S**)-4-Dimethoxymethylbicyclo[3.2.0]hept-2-en-7-one (2)**

A solution of compound **1** (1.0 g, 5.5 mmol) in oxygen free ethyl acetate (200 mL) was irradiated under a nitrogen atmosphere with a 450-W medium pressure mercury lamp using a Pyrex glass filter for 8 h. The solution was concentrated, and the residue was purified by flash column chromatography on silica gel (elution with 12:1 hexane/ethyl acetate) to yield compound **2** (0.78 g, 78%) as a colorless oil. IR ($CHCl_3$) 1777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85-5.77 (m, 1H), 5.74-5.70 (m, 1H), 4.47 (d, J = 8.4 Hz, 1H), 4.25-4.15 (m, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.35-3.29 (m, 1H), 3.22 (dt, J = 3.3, 11.7 Hz, 1H), 3.03-2.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.65 (s), 133.63 (d), 127.64 (d), 103.88 (d), 73.60 (d), 53.72 (q), 52.60 (q), 50.71 (d), 46.97 (t), 27.67 (d); LRMS (EI, 30 eV); 182 (M^+, 2.1), 91 (100); HRMS calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0945.

(1*R,4*S**,5*R**)-4-Dimethoxymethylbicyclo[3.3.0]oct-2-en-7-one (3) and (1*R**,4*S**,5*S**)-4-dimethoxymethylbicyclo-[3.3.0]oct-2-en-8-one (4)**

A solution of **2** (2.0 g, 10.99 mmol) and methanol (1 mL) in ether (40 mL) was treated with excess diazomethane (generated from Diazald) at 0 °C. After 16 h, nitrogen was bubbled into the solution to remove excess diazomethane. The ether solution was concentrated and the residue chromatographed on silica gel (elution with 12:1 hexane/ethyl acetate) to afford **3** (1.09 g, 51%) and **4** (0.72 g, 33%). For **3**: colorless oil; IR ($CHCl_3$) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73-5.65 (m, 2H), 4.22 (d, J = 8.4 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.38-3.28 (m, 1H), 3.23-3.15 (m, 1H), 3.03-2.92 (m, 1H), 2.40 (dd, J = 9.3, 19.2 Hz, 1H), 2.70 (d, J = 3.0 Hz, 1H), 2.22 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.11 (s), 135.48 (d), 130.54 (d), 104.85 (d), 53.40 (q, 2C), 51.05 (d), 46.30 (d), 41.95 (t), 39.96 (d), 38.68 (t); LRMS (EI, 30 eV) 196 (M^+, 0.04), 75 (100); HRMS calcd for $C_{11}H_{16}O_3$ 196.1100, found 196.1107. For **4**: colorless oil; IR ($CHCl_3$) 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69-5.62 (m, 2H), 4.38 (d, J = 6.3 Hz, 1H), 3,37 (s, 3H), 3.36 (s, 3H), 3.43-3.27 (m, 1H), 3.30-3.15 (m, 1H), 3.00-2.88 (m, 1H), 2.21 (dd, J = 9.0, 3.3 Hz, 2H), 2.05-1.94 (m, 1H), 1.78-1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.50 (s), 132.06 (d), 128.71 (d), 103.55 (d), 60.18 (d), 52.94 (q), 52.72 (q), 51.30 (d), 40.44 (d), 39.21 (t), 22.41 (t); mass (EI, 30 eV) 196 (M^+, 1.21), 75 (100); HRMS calcd for $C_{11}H_{16}O_3$ 196.1100, found 196.1105.

Methyl (1*R,4*S**,5*R**)-8-oxobicyclo[3.3.0]oct-2-ene-4-carboxylate (6)**

A solution of **4** (0.50 g, 2.55 mmol) in acetone (20 mL) was treated with excess Jones reagent at 0 °C. The mixture was stirred for 30 min and treated with isopropanol to destroy the unreacted oxidant. After the solvent was removed, the residue was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried, and concentrated. The residue was dissolved in ether (20 mL) and treated with excess diazomethane at 0 °C. After 15 min, nitrogen was bubbled into the solution to remove excess diazomethane followed by concentration. The residue was purified by column chromatography on silica gel (elution with 12:1 hexane/ethyl acetate) to give **6** (0.28 g, 61%) as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.90-5.86 (m, 1H), 5.77-5.73 (m, 1H), 3.91-3.87 (m, 1H), 3.74 (s, 3H), 3.37-3.25 (m, 2H), 2.30-2.22 (m, 3H), 1.63-1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.61 (s), 172.36 (s), 130.25 (d), 129.36 (d), 59.60 (d), 54.24 (d), 51.53 (q), 40.35 (d), 38.44 (t), 23.66 (t); mass (EI, 30 eV) 180 (M^+, 11.97), 92 (100); HRMS calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0790.

Methyl (1*R,4*S**,5*R**)-7-oxobicyclo[3.3.0]oct-2-ene-4-carboxylate (5)**

To a solution of **3** (0.80 g, 4.08 mmol) in acetone (20 mL) was added excess Jones reagent at 0 °C. The mixture was stirred for 30 min and treated with isopropanol to destroy the unreacted oxidant. After the solvent was removed, the residue was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried, and concentrated. The residue was dissolved in ether (20 mL) and treated with excess diazomethane at 0 °C. After 15 min, nitrogen was bubbled into the solution to remove excess diazomethane followed by concentration. The residue was purified by column chromatography on silica gel (elution with 12:1 hexane/ethyl acetate) to afford **5** (0.52 g, 71%) as a light yellow oil: IR (neat) 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87-5.84 (m, 1H), 5.81-5.78 (m, 1H), 3.88-3.84 (m, 1H), 3.70 (s, 3H), 3.48-3.45 (m, 1H), 3.32-3.26 (m, 1H), 2.52-2.27 (m, 3H), 2.05 (dd, J = 18.0, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.85 (s), 173.01 (s), 136.20 (d), 129.00 (d), 54.20 (d), 51.77 (q), 46.25 (d), 42.33 (t), 40.72 (d), 39.99 (t); mass (EI, 70 eV) 180 (M^+, 26.13), 79 (100); HRMS calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0786.

(3a*S,4*S**,6a*R**)-4-Dimethoxymethyl-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]oxol-2-one (12)**

A suspension of MCPBA (2.39 g, 13.82 mmol) and $NaHCO_3$ (9.69 g, 115.34 mmol) in dichloromethane (50 mL)

was stirred for 1 h. Compound **9** (2.10 g, 11.54 mmol) was added to the mixture and stirred for an additional 3 h. The precipitate was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (elution with 5:1 hexane/ethyl acetate) to yield **12** (2.18 g, 96%) as an oil: IR ($CHCl_3$) 1771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01-5.97 (m, 1H), 5.96-5.90 (m, 1H), 5.46-5.40 (m, 1H), 4.24 (d, J = 7.2 Hz, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 3.25-3.10 (m, 2H), 2.58 (d, J = 1.8 Hz, 1H), 2.56 (d, J = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.02 (s), 136.19 (d), 130.29 (d), 104.64 (d), 88.33 (d), 54.20 (q), 53.86 (q), 49.47 (d), 37.77 (d), 29.89 (t); mass (EI, 70 eV) 197 (M^+-1, 0.43), 75 (100); HRMS calcd for $C_{10}H_{13}O_4$ 197.0814 (M^+-1), found 197.0821.

(1*R,5*R**)-6-oxobicyclo[3.2.0]hept-2-ene-2-carbaldehyde (14)**

To a solution of **2** (1.00 g, 5.49 mmol) in THF (15 mL) and acid chloride (2 N, 5 mL) was stirred at room temperature for 3 h. The mixture was made basic with an aqueous solution of saturated sodium bicarbonate at 0°C and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After the evaporation of the solvent, the residue was chromatographed on silica gel (elution with 4:1 hexane/ethyl acetate) to obtain **14** (0.42 g, 62%) as a colorless oil: IR ($CHCl_3$) 2840, 1780 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 6.90 (s, 1H), 4.08-3.96 (m, 1H), 3.76-3.68 (m, 1H), 3.60-3.45 (m, 1H), 2.97 (dd, J = 19.8, 2.1 Hz, 1H), 2.87-2.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.46 (s), 188.93 (d), 152.34 (d), 148.83 (s), 62.07 (d), 54.55 (t), 35.06 (t), 33.90 (d); mass (EI, 30 eV) 136 (M^+, 1.55), 66 (100); HRMS calcd for $C_8H_8O_2$ 136.0525, found 136.0522.

(3a*S,6a*R**)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]-oxole-4-carboxylate (13)**

A suspension of MCPBA (0.33 g, 1.91 mmol) and $NaHCO_3$ ($NaHCO_3$, 1.60 g, 19.04 mmol) in dichloromethane (20 mL) was stirred for 1 h. Compound **14** (0.26 g, 1.91 mmol) was added to the mixture and stirred for an additional 3 h. The precipitate was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (elution with 4:1 hexane/ethyl acetate) to yield **13** (0.15 g, 52%) as an oil: IR ($CHCl_3$) 2843, 1775, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 6.88 (d, J = 1.8 Hz, 1H), 5.25-5.15 (m, 1H), 3.80-3.65 (m, 1H), 3.05-2.95 (m, 2H), 2.87 (dd, J = 18.9, 9.9 Hz, 1H), 2.69 (dd, J = 18.9, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.59 (d), 175.89 (s), 149.65 (d), 145.74 (s), 82.01 (d), 43.18 (d), 40.36 (t), 31.98 (t); mass (70 eV) 152 (M^+, 3.5), 79 (100); HRMS calcd for $C_8H_8O_3$ 152.0473, found 152.0469.

ACKNOWLEDGMENTS

We thank the National Science Council of the Republic of China for financial support and Professor Renaud (Institute de Chimie Organique, University of Fribourg) for sending spectral data of compound **13** to us for comparison.

Received March 26, 2001.

Key Words

Cyclopentanoid natural products; Iridoid monoterpenes; Prostaglandins; Photochemical rearrangement.

REFERENCES

1. For reviews see: (a) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507. (b) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Heideberg, 1987, 112. (c) ApSimon, J. *The Total Synthesis of Natural Products*; Wiley: New York, 1988, Vol 7; 339. (d) ApSimon, J. *The Total Synthesis of Natural Products;* Wiley: New York, 1981, Vol 4; 494. (e) ApSimon, J. *The Total Synthesis of Natural Products*; Wiley: New York, 1973, Vol 2; 62.
2. Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Heideberg, 1987, 127.
3. Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Heideberg, 1987, 169.
4. (a) Demuth, M.; Schaffner, K. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 820. (b) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Heideberg, 1987, 112.
5. (a) Hewson, A. T.; MacPherson, D. T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2625. (b) Hewson. A. T.; MacPherson, D. T. *Tetrahehron Lett.* **1983**, 5807. (c) Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1293. (d) Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 3585. (e) Tai, H.-M.; Yang, C.-C.; Chang, N.-C. *J. Chin. Chem. Soc.* **1995**, *42*, 821.
6. (a) Greene, A. E.; Depres, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003. (b) Greene, A. E.; Depres, J.-P. *J. Org. Chem.* **1980**, *45*, 2037. (c) Hassner, A.; Pinnick, H. W.; Ansell, J.

M. *J. Org. Chem.* **1978**, *43*, 1774.
7. Ghosez, L. *Tetrahedron* **1971**, *27*, 615.
8. (a) Schenck, G. O.; Steinmetz, R. *Chem. Ber.* **1963**, *96*, 520. (b) Schuster, D. I.; Axelrod, M.; Au er bach, J. *Tetrahe dron Lett.* **1963**, 1911. (c) Bays, D. E.; Cookson, R. C. *J. Chem. Soc. B.* **1967**, 226. (d) Scharf, H.-D.; Kusters, W. *Chem. Ber.* **1971**, *104*, 3016. (e) Ipaktsohi, J. *Chem. Ber.* **1972**, *105*, 1840. (f) Hwu, J. R.; Gilbert, B. A.; Lin, L. C.; Liaw, B. R. *J. Chem. Soc., Chem. Commun.* **1990**, 161.
9. Chang, N.-C.; Day, H.-M.; Lu, W.-F. *J. Org. Chem.* **1989**, *54*, 4083 and ref er ences cited therein.
10. (a) Hsu, L.-F.; Chang, N.-C. *J. Chin. Chem. Soc.* **1994**, *41*, 609. (b) Tai, H.-M.; Chang, M.-Y.; Lee, A.-Y.; Chang, N. C. *J. Org. Chem.* **1999**, *64*, 659 and ref er ences cited therein.
11. (a) Chang, C.-P.; Yin, W.-K.; Chang, N.-C. *J. Chin. Chem. Soc.* **1994**, *41*, 613. (b) Tai, H.-M.; Yang, C.-C. *J. Chin. Chem. Soc.* **2000**, *47*, 929 and references cited therein.
12. Hsu, L.-F.; Chang, C.-P.; Li, M.-C.; Chang, N.-C. *J. Org. Chem.* **1993**, *58*, 4756 and ref er ences cited therein.
13. Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972.
14. Vionnet, J.-P.; Renaud, P. *Helv. Chim. Acta* **1994**, *77*, 1781.
15. (a) Crabbe, P.; Guzman, A.; Vera, M. *TetrahedronLett.* **1973**, 4730. (a) Sala, R.; Doria, G.; Passarotti, C. *Tetrahe dron Lett.* **1984**, 4565. (b) Corey, E. J.; Snider, B. B. *J. Org. Chem.* **1974**, *39*, 256. (d) Lai, S.; Lee, D.; Sun, J. U.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 7213.
16. Schenider, W. P.; Morge, R. A. *TetrahedronLett.* **1976**, 3283.