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2-Pupukeanone, 9-Pupukeanone, 9-Isocyanoneopupukeanane , Isoclovene, Capnellene 和 Hirsutene 的合成研究

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Abstract:

A total synthesis of (±)-hop ether (**2**) is described. The key steps include regioselective tosylation of triol **8** followed intramolecular ring closure to form **9** and photolytic cleavage of bicyclo[2.2.1]heptannone **5**.

Treatment of 3,4-dihydro-5-sulfonylpyridin-2-ones with PCC gave the corresponding pyridin-2-ones. Formal synthesis of mappicine ketone, base promoted double elimination of 5-hydroxy-4-sulfonyl lactam, was also reported.

Key Words: hop ether; iridoid monoterpene; cyclopenta[c]pyran; glutarimide; pyridin-2-one; mappicine ketone;

Total Synthesis of (±)-Hop Ether

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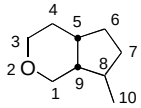
Key Words: hop ether; iridoid monoterpene; cyclopenta[c]pyran.

Introduction:

The iridoid monoterpenes represent a large family of cyclopentanopyran natural products.[1] Among the varies iridoids, the cyclopenta[*c*]pyran bearing the 2-oxo-*cis*-bicyclo[4.3.0]nonane **1** (scheme I) moiety as a fundamental ring system is the most widely distributed.[2] Hop ether (**2**),[3] isolated from Japanese hops,[4] is one of the most simplest iridoids. It occupies an unique position in the iridoid monoterpenes due to it is the most straigthforard one, in a biogenetical sense, from the geraniol (**3**) precursor and it has no functional group on both of isopropyl methyl groups of the iridane skeleton Herein, we describe a total synthesis of racemic hop ether.

Scheme I



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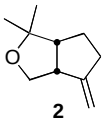

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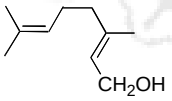

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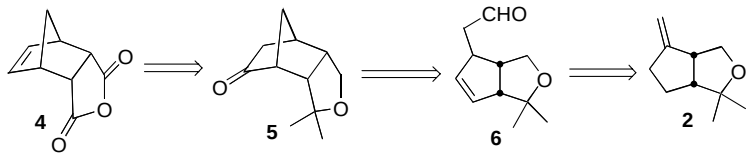
Result and Discussion:

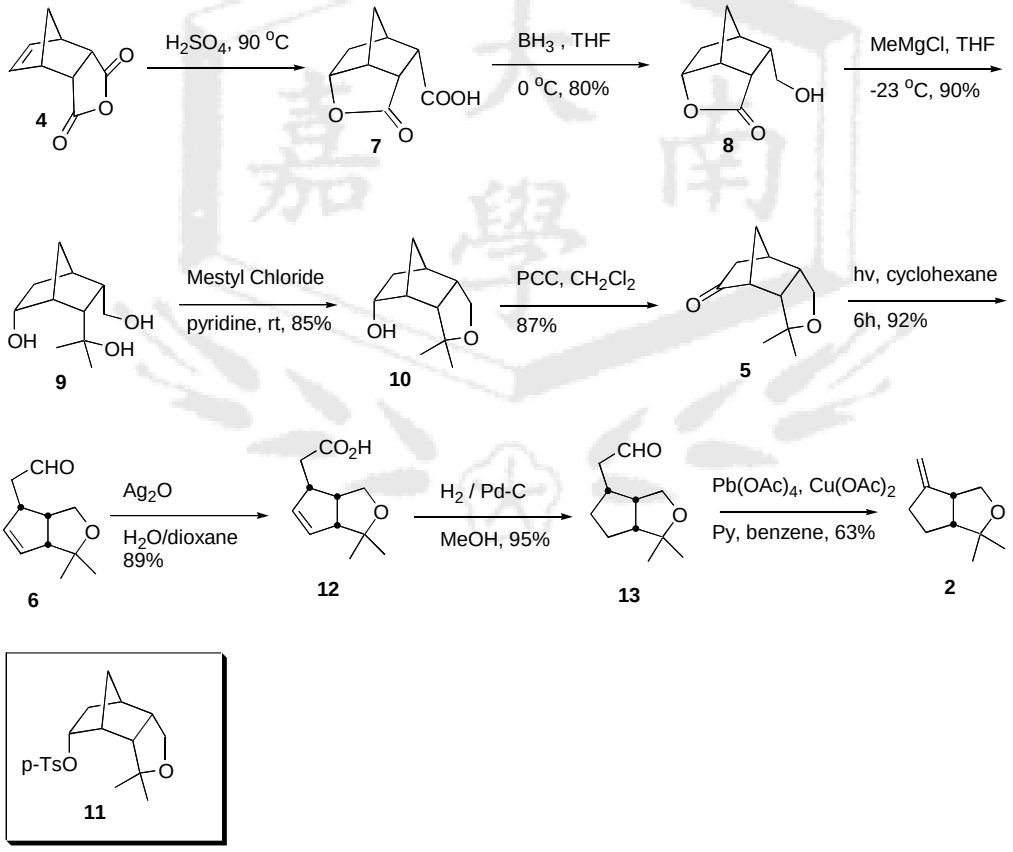
Our synthesis strategy is outline in scheme II, the crucial steps include (1) conversion of anhydride **4** into ketone **5**; (2) perform a Norrish type I reaction on ketone **5** to produce aldehyde **6**. The compound **6** is a reasonable precursor for the synthesis of hop ether (**2**).

Scheme II



Lactone **7**, easily prepared from the known Diels-Alder adduct **4** by hydration with concentrated sulfuric acid, was chosen as starting material.[5] Reduction of the acid group in **7** with diborane in THF gave the corresponding hydroxyl ester **8** (80%).[6] The spectra data of compound **8** was high agreed with those of literature reported.[7] Treatment of **8** with excess methyl magnesium chloride at 0 ^{o}C afforded triol **9** (90%). When triol **9** reacted with para-toluenesulfonyl chloride to yield **10** (42%) and tosylate **11** (35%). The structure of **11** was confirmed by X-ray analysis. After great efforts, triol **9** was successfully transformed into **10** (85%) with mestyl chloride in pyridine. Alcohol **10** then reacted with pyridium chlorochromate to furnish the corresponding bicyclo[2.2.1]heptanone **5** in 87% yield.

Scheme III



Photolysis of **5** produced the Norrish type I cleavage product **6** (92%). With compound **6** in hand, its conversion to target molecule is quite straightforward. Oxidation of the formyl group in **6** with silver oxide in methanolic aqueous solution afforded the acid **12** (89%), which was subsequently catalytic hydrogenation to yield **13** (95%). Finally one carbon degradation of **13** was achieved by treating of **12** with

lead tetraacetate in presence of copper (II) acetate to furnish hop ether (**2**) in 63% yield. The structure of **2** was confirmed by comparison of the ^{1}H and ^{13}C NMR spectra with those of an authentic sample provided by reported literature.[8]

In conclusion, we have developed a facile route to synthesis of hop ether (**2**). Efforts directed toward the synthesis of other naturally occurring terpenes are currently under way in our laboratory.

Experimental section:

All reagents and solvents were obtained from commercial sources and used without further purification. A column chromatograph contained silica gel (70~230 mesh); precoated TLC sheets of silica gel (60 f_{254} plates) were used for thin-layer chromatography. 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. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 200 spectrometer, with TMS as the internal standard. Mass spectra (MS) were measured on a VGQUATTRO 5022 mass spectrometer. High resolution mass (HRMS) values were determined on a JEOL JMSHY 110 mass spectrometer. Elemental analyses (EA) were performed on a Heraeus CHN-O analyzer.

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An efficient Route to Pyridin-2-ones.

Formal Synthesis of Mappicine Ketone

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Abstract: Treatment of 3,4-dihydro-5-sulfonylpyridin-2-ones with PCC gave the corresponding pyridin-2-ones. Formal synthesis of mappicine ketone, base promoted double elimination of 5-hydroxy-4-sulfonyl lactam, was also reported.

Introduction:

Alkaloids with six-membered nitrogen contained ring systems have a wide and varied distribution in nature.[1] Theses compounds display a broad range of interesting biological activities, and many of them serve as intermediates in the synthesis of more elaborate compounds.[2] It is known that pyridin-2-one ring system is a valuable building block in natural product synthesis.[3] Numerous methods for the preparation of substituted pyridin-2-one have been reported in the literatures.[4] Recently, we reported a general method which regioselectively reduced the carbonyl group on 3-sulfonyl glutarimides to the corresponding hydroxylactams, which were further dehydrated to 3,4-dihydropyridin-2-ones in the presence of boron trifluoride.[5] Herein, we reported the synthesis of 4,5-disubstituted- 3-sulfonyl glutarimides and an efficient access to a variety of substituted pyridin-2-ones. A formal synthesis of mappicine ketone is also reported.

Results and Discussion:

Synthesis of 4,5-disubstitued-3-sulfonyl glutarimides Previously we reported a stepwise [3+3] cycloaddition to 4- or 5-monosubstitued- 3-sulfonyl glutarimides **3** by the sequence reaction of α-sulfonyl acetamide (**1**) and α,β-unsaturated esters **2** in good to excellent yields.[5] However, the synthesis 4,5-disubstitued-3-sulfonyl glutarimides **3** got poor yields in the same condition. After great efforts, 4,5-disubstitued-3-sulfonyl glutarimides **3** were successfully contributed with

α-sulfonyl acetamide and α,β-unsaturated esters (4 eq.) in presence 3 eq. of sodium hydride in THF at 55 ^{o}C in moderate to good yields. Several examples were examined and results are listed in table I.

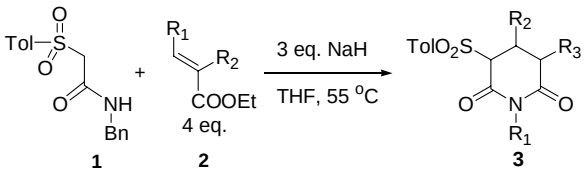


Table 1: Cycloaddition reactions to form 4,5-disubstitued-3-sulfonyl glutarimides

Entry	R_1	R_2	R_3	**3**, Yield (%)
1	—Bn	—CH_3	—CH_3	71
2	—Bn	—$CH(OCH_3)_2$	—CH_3	40
3	—Bn	—$CH_2CH_2CH_3$	—CH_3	65
4	—Bn	—CH_2OBn	—CH_3	42
5	—Bn	—$CH(OCH_3)_2$	—CH_2CH_3	43
6	—PMB	—CH_3	—CH_3	75

New approach to pyridin-2-ones We further developed an efficient approach to 3-or 4-substituted pyridin-2-ones **5**. Oxidative demethoxybenzylation of **4** with CAN gave the corresponding 3,4-dihydropyridin-2-ones,[6] which further oxidized to afford 5-sulfonyl pyridin-2-ones **5**. The results are given in table II.

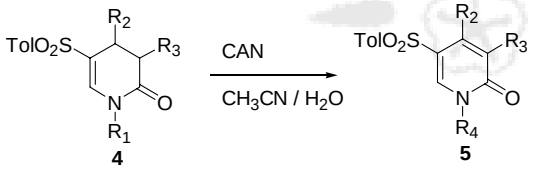
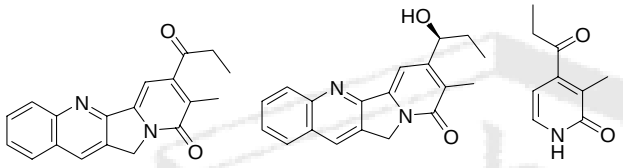


Table II: Synthesis of 5-sulfonyl pyridin-2-ones

Entry	R_1	R_2	R_3	R_4	**5**, Yield (%)
1	—Bn	—CH_3	—H	—Bn	89
2	—Bn	—$CH(OCH_3)_2$	—H	—Bn	56
3	—Bn	—Ph	—H	—Bn	70
4	—Bn	—H	—CH_3	—Bn	86
5	—PMB	—CH_3	—H	—H	79
6	—PMB	—Ph	—H	—H	75
7	—Bn	—CH_3	—CH_3	—Bn	20
8	—PMB	—CH_2OBn	—CH_3	—H	15

Synthesis of mappicine ketone. Mappicine ketone (**6**) is a derivative of a natural alkaloid mappicine (**7**), isolated from *Mapia foetida* Miers.[7] It has been reported that **6** possess potent activity against the herpes viruses HSV-1 and HSV-2 and human cytomegalovirus (HCMV).[8] To demonstrate the potential of above method to synthesis of pyridin-2-ones, we will synthesis the compound **8** has been reported a reasonable precursor of mappicine ketone.[9] Surprisingly, Oxidative dehydrogenation of 3,4-dihydropyridin-2-ones with CAN gave the corresponding 3,4-disubstituted-5-sulfonyl pyridin-2-ones in low yields. We were unable to obtain useful amounts of the pyridone to transformation to mappicine precursor.

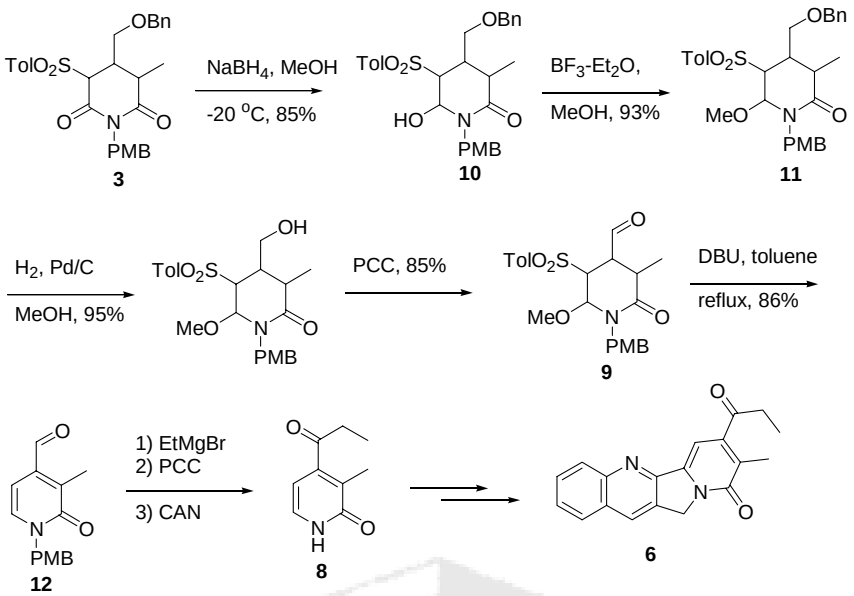


6 **7** **8**

Revised synthetic method of mappicine ketone We anticipated that pyridone could be carried out by double elimination of **9**. The synthesis of mappicine ketone was carried out as depicted in scheme I. Regioselective reduction of **3** with sodium borohydride at –20 ^{o}C obtained hydroxylactam **10**. Without further purification, subsequent acid acetylation of **10** afforded methoxy sulfonyl lactam **11** in 90% yield. Functional group transformation of protected primary alcohol to aldehyde **9** was achieve by catalytic debenzylation followed PCC oxidation of **11**, Base promoted double elimination of 5-hydroxy-4-sulfonyl lactam **11** with DBU furnished pyridone **12** in 86% yield. Ethyl Griganrd addition to the formyl group of **12**, the resulting secondary alcohol was oxidized to ketone with PCC. Finally, The PMB group was removed to afford pyridone **8**. As reported,[9] pyridone **8** has been converted to mappicine ketone (**6**).

In summary, we have developed a facile route to 4,5-disubstitued-3-sulfonyl glutarimides **3** and 3-or 4-substituted pyridin-2-ones **5**. Formal synthesis of mappicine ketone was also successfully performed by double elimination of 5-hydroxy-4-sulfonyl lactam **11**. The application of this result in the synthesis of alkaloids is currently under in our laboratory.

Acknowledgment Financial support from the National Science Council of the Republic of China is gratefully acknowledged.



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