HETEROCYCLES, Vol. 68, No. 2, 2006, pp. 271 - 282. © The Japan Institute of Heterocyclic Chemistry
Received, 4th November, 2005, Accepted, 12th December, 2005, Published online, 13th December, 2005. COM-05-10612

FORMAL SYNTHESIS OF (±)-HOP ETHER, (±)-ISOBOONEIN, AND (±)-IRIDOMYRMECIN

Meng-Yang Chang,*[,a] Ru-Ting Hsu,[b] Chun-Yu Lin,[a] Bor-Fong Chen,[c] Shiang-Tsern Lin,[d] and Nein-Chen Chang*[,c]

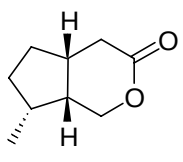
[a]*Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan* [b]*Department of Nursing, Shu-Zen College of Medicine and Management, Kaohsiung 821, Taiwan* [c]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan* [d]*Department of Nutrition, Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

Abstract—A general synthesis of (±)-hop ether (**5**), (±)-isoboonein (**6**), and (±)-iridomyrmecin (**7**) from bicyclo[2.2.1]ketone (**9**) is described. Cyclopentenoid aldehyde (**10**) and bicyclo[3.2.1]lactone (**11**) are the key intermediates.

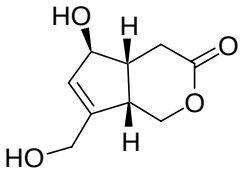
INTRODUCTION

The iridoids are a large class of naturally occurring compounds with over 300 members in the family. They are characterized by a cyclopentane or cyclopentene ring *cis*-fused to a δ-lactone, dihydropyran or dihydrofuran.[1] Irido monoterpenoids with a cyclopentane ring are important because of their diverse and interesting physiological and biological activities.[2] The major challenge on the synthesis of iridoid monoterpenoids was to provide the installation of contiguous stereogenic chiral centers on their molecular system employing some various approaches and useful methodologies during three decades.

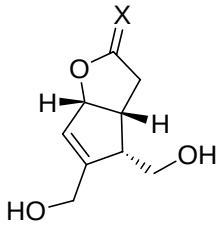
Figure 1.



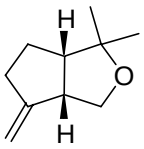
boschnialactone (**1**)



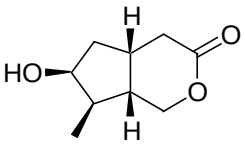
iridolactone (**2**)



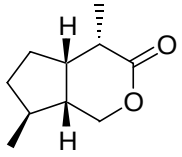
X=O, pedicularis-Lactone (**3**)
X=H_2, ningpogenin (**4**)



hop ether (**5**)



isoboonein (**6**)



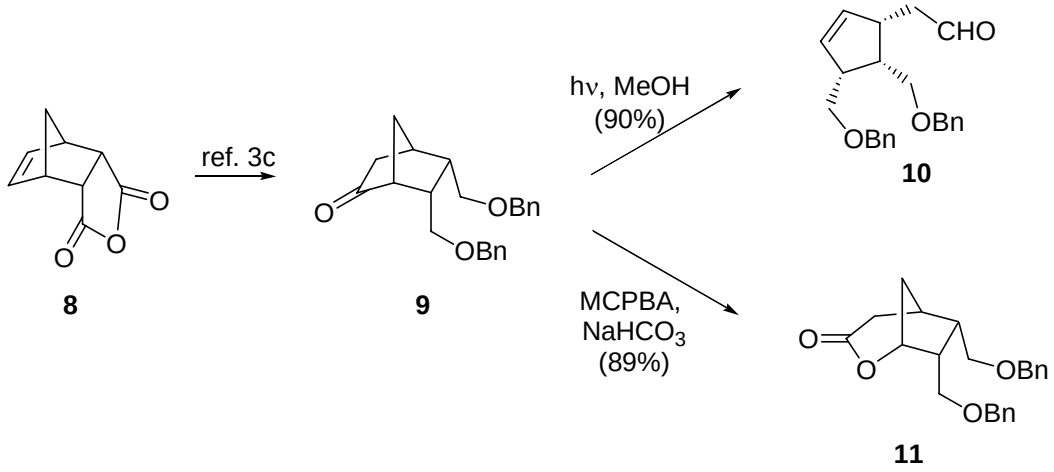
iridomyrmecin (**7**)

Previously, we have reported a facile and straightforward synthesis of (±)-boschnialactone (**1**),[3a] (±)-iridolactone (**2**),[3b] (±)-pedicularis-lactone (**3**),[3c] and (±)-ningpogenin (**4**)[3c] *via* the key step of Norrish type 1 photolytic cleavage as shown in Figure 1. To demonstrate the synthetic utility of the methodology and continue our investigation on the application of this straightforward approach, the synthesis of (±)-hop ether (**5**), (±)-isoboonein (**6**), and (±)-iridomyrmecin (**7**) was studied. Their related significant features are described as follows. Hop ether (**5**) was first isolated and characterized from the volatile constituents of Japanese hop "Shinshu-wase" by Naya and Kotake[4] in 1967. Hop ether (**5**) is regarded as a component which markedly affects the aroma and taste of beer[5] and has attracted considerable interest from synthetic chemists.[6] Isoboonein (**6**)[7a] was an analog of boonein[7b] and it was isolated from *Rauwolfia grandiflora* by Bianco and coworkers. To date, there are few reports for the synthesis of isoboonein (**6**) citations[8] and its related biological activities has not also been reported. Iridomyrmecin (**7**) exhibited strong insecticide activities against preying insects from ants (*Iridomyrmex humilis*)[9] and a lot of related synthetic reports have been published.[10]

RESULTS AND DISCUSSION

Here we report that a general synthesis toward (±)-hop ether (**5**), (±)-isoboonein (**6**), and (±)-iridomyrmecin (**7**) has been established by synthesizing aldehyde (**10**) and lactone (**11**) *via* Norrish type 1 photolytic cleavage[11] and Baeyer-Villiger ring-expanded lactonization of bicyclo[2.2.1]ketone (**9**).[12] Ketone (**9**) was yielded from anhydride (**8**) in overall 60% yield of four steps (Scheme 1).[3c]

Scheme 1.

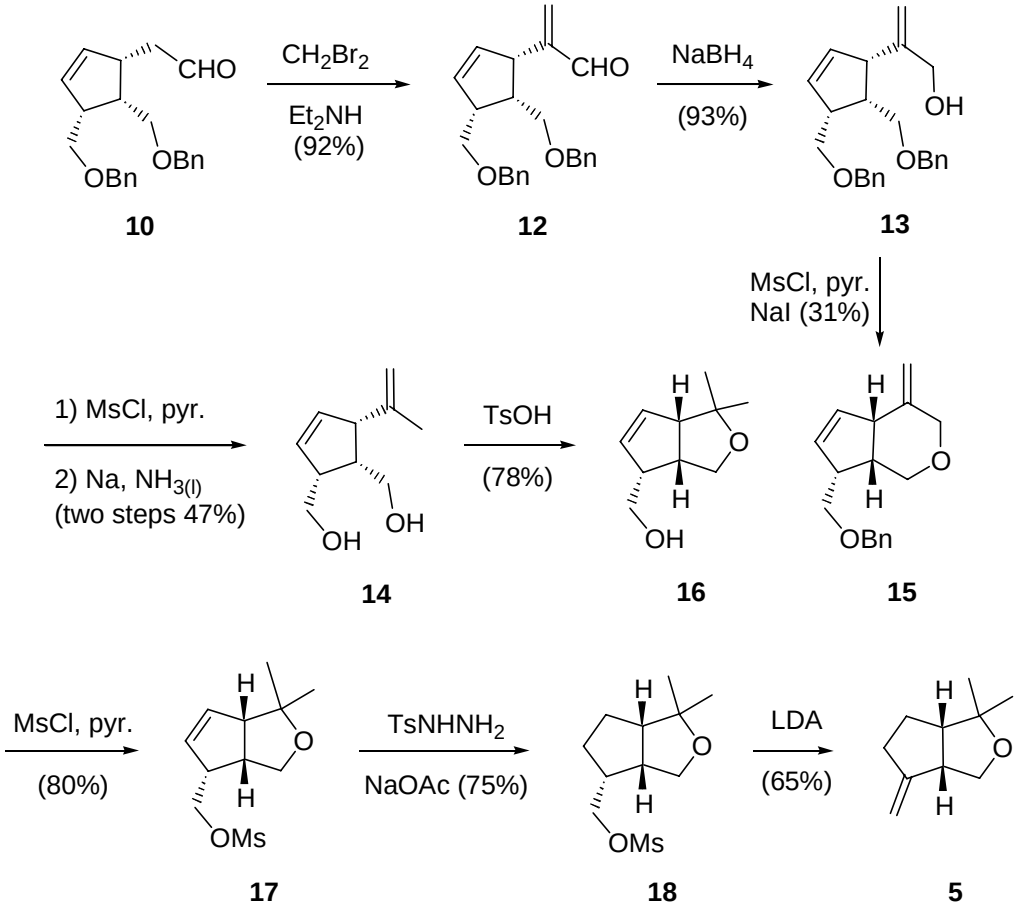


8 **9** **10** **11**

As shown in Scheme 2, sole aldehyde (**10**) was afforded in better yield *via* Norrish type 1 photolytic cleavage (λ>310 nm) of ketone (**9**) in methanol. Treatment of aldehyde (**10**) with diethylamine and dibromomethane under Hon's condition[13] gave a α-methylene aldehyde (**12**) which further reacted with sodium borohydride in methanol to yield allylic alcohol (**13**). Compound (**13**) was transformed into diol (**14**) by mesylation and Birch reduction under standard conditions. During the mesylation procedure, a mixture of mesylate and chloride compounds was yielded in different ratio. Without further purification,

the resulting mixture was reacted directly with sodium and liquid ammonia to provide diol (**14**). In order to provide sole compound and decrease the complexity of products during the mesylation procedure, sodium iodide was added to the reaction mixture and the bicyclic skeleton (**15**) was isolated in only 31% yield *via* a cyclization. This result was unexpected.

Scheme 2.



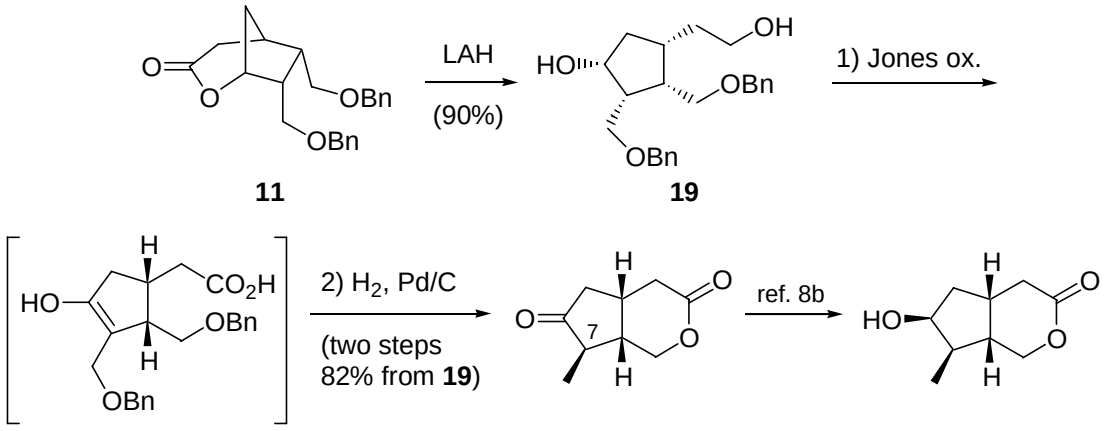
With diol (**14**) in hand, treatment of diol (**14**) with a catalytic amount of *p*-toluenesulfonic acid in tetrahydrofuran gave a bicyclo[3.3.0]octane skeleton (**16**) by a cyclization. During the ring closure process, the fused bicyco[3.2.1]octane framework was not observed. Reduction of olefinic group on compound (**16**) with hydrogen in the presence of different transition metal catalyst was yielded complex products. The desired saturated alcohol compound was only generated in trace yield (<5%). The possible reaction mechanism has been proposed as follows. Presumably, once an allylic alcohol was formed under double bond isomerization, the further allylic reduction proceeded in the catalytic hydrogenation reaction. In order to increase the yield of desired product and reduce the opportunity of allylic reduction, the diimide reduction was chosen as the next step.

Mesylation of olefin (**16**) with methanesulfonyl chloride and pyridine gave mesylate (**17**). Treatment of mesylate (**17**) with 4-toluenesulfonylhydrazine and sodium acetate gave compound (**18**) in modest yield. When the synthetic sequence of mesylation and reduction was exchanged, compound (**18**) was generated in only 21% yield of two-step from compound (**16**). Attempts to form *exo*-olefin were unsuccessful under

a variety of basic conditions. Finally, elimination of mesylate group by lithium diisopropylamide at reflux temperature gave (±)-hop ether (**5**). A total synthesis of (±)-hop ether (**5**) was achieved.

For the synthetic study of (±)-isoboonein (**6**), compound (**11**) was chosen as starting material. Baeyer-Villiger ring expansion of ketone (**9**) should be affected by the neighboring oxygen atom of benzyl group under basic condition to produce sole lactone (**11**) with good regioselectivity. Another ring-expanded lactone was not obtained in the reaction condition. As shown in Scheme 3, treatment of lactone (**11**) with lithium aluminum hydride gave a diol (**19**). Jones oxidation of diol (**19**) gave keto acid which further reacted with hydrogen and 10% palladium on activated carbon in methanol to yield single product (**21**) *via* the formation of the proposed intermediate (**20**). The ^{1}H and ^{13}C NMR spectral data of compound (**21**) was in accordance with the reported in the literature.[8b] Presumably, methyl group was easy to epimerize into *exo* face during the acid-mediated allylic hydrogenation. The stereochemical selectivity of methyl group at C-7 was well established. Here we provided a simple four-step synthetic route toward synthesis of compound (**21**) from known ketone (**9**). Compound (**21**) was converted to (±)-isoboonein (**6**) from a known two-step procedure.[8b] A formal synthesis of (±)-isoboonein (**6**) was accomplished.

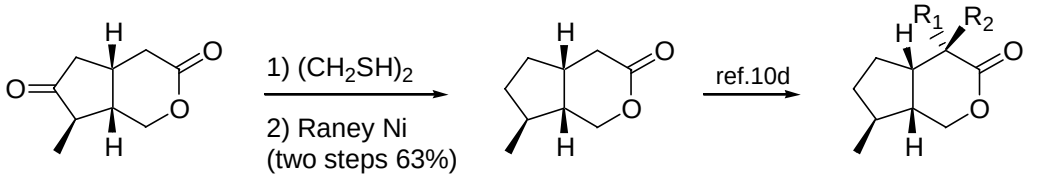
Scheme 3.



11 **19** **20** **21** **6**

We next turn our focus toward the formal synthesis of (±)-iridomyrmecin (**7**) *via* a mild two-step reductive deoxygenation reactions from ketone (**21**) (Scheme 4): (i) protection of ketone (**21**) with 1,2-ethanedithiol and boron trifluoride etherate, (ii) deprotection of the resulting compound with Raney nickel. Lactone (**22**) was converted to (±)-iridomyrmecin (**7**) and (±)-isoiridomyrmecin (**23**) using the alkylation reaction.[10d]

Scheme 4.



21 **22**

7, R_1=Me, R_2=H
23, R_1=H, R_2=Me

CONCLUSION

In summary, we have developed a straightforward approach to synthesis of (±)-hop ether (**5**), (±)-isoboonein (**6**), and (±)-iridomyrmecin (**7**) based on Norrish photolytic cleavage and Baeyer-Villiger lactonization of bicyclo[2.2.1]ketone (**9**) as the key step. We are currently studying the scope of this process as well as additional applications of this approach to the synthesis of various potential biological activities compounds using chiral bicyclo[2.2.1]ketone (**9**) as the starting material.

EXPERIMENTAL

General. Dichloromethane and tetrahydrofuran were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. All reported melting temperatures are uncorrected.

2-(4,5-Bisbenzyloxymethylcyclopentenyl)acetaldehyde (10).[3c]

Ketone (**9**) (1.0 g, 2.9 mmol) dissolved in methanol (200 mL) free of oxygen was irradiated under a nitrogen atmosphere with a lamp (λ>310 nm), using a pyrex glass filter at rt for 15 h. The solvent was evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 10/1) yielded aldehyde (**10**) (0.9 g, 90%) as a colorless oil: IR (neat) 3031, 2857, 2716, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.67-9.66 (m, 1H), 7.36-7.25 (m, 10H), 5.83-5.80 (m, 1H), 5.75-5.73 (m, 1H), 4.45-4.31 (m, 4H), 3.61 (dd, *J* = 6.6, 9.3 Hz, 1H), 3.40 (t, *J* = 9.3 Hz, 1H), 3.37 (d, *J* = 5.4 Hz, 2H), 3.30-3.20 (m, 1H), 3.00-2.90 (m, 1H), 2.83-2.72 (m, 1H), 2.60 (ddd, *J* = 2.4, 6.9, 16.5 Hz, 1H), 2.35 (ddd, *J* = 1.5, 7.8, 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.12, 138.10, 134.71, 132.19, 128.32 (3x), 127.88 (3x), 127.79 (3x), 127.61 (2x), 73.20, 72.95, 70.53, 67.86, 46.98, 46.09, 41.75, 40.60; Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48; Found: C, 78.83; H, 7.34.

2-(4,5-Bisbenzyloxymethylcyclopent-2-enyl)propenal (12).

A solution of aldehyde (**10**) (2.4 g, 6.86 mmol) in dichloromethane (20 mL) was added to the stirred mixture of diethylamine (12.5 g, 171.23 mmol) and dibromomethane (23.8 g, 136.78 mmol). The reaction mixture was heated to 55 °C for 16 h and concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 4/1) yielded α,β-unsaturated aldehyde (**12**) (2.28 g, 92%) as a viscous oil: IR ($CHCl_3$) 1690, 1635, 1097 cm^{-1}; EI-MS (30 eV) $C_{24}H_{26}O_3$ m/z (%) = 91 (100), 363 (M^++1, 1); ^1H NMR (500 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.33-7.20 (m, 10H), 6.08 (s, 1H), 5.98 (dt, *J* = 2.5,

6.0 Hz, 1H), 5.93 (s, 1H), 5.60 (dt, *J* = 2.5, 6.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 4.23 (dd, *J* = 11.5 Hz, 1H), 3.98 (d, *J* = 8.5 Hz, 1H), 3.53 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.37 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.32-3.24 (m, 2H), 3.12-3.09 (m, 1H), 2.99-2.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.21, 150.13, 138.32, 138.15, 134.69, 134.35, 131.63, 128.30 (2x), 128.25 (2x), 127.79 (2x), 127.70 (2x), 127.56, 127.45, 73.06, 72.82, 70.58, 68.00, 47.48, 44.09, 42.54; Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23; Found: C, 79.82; H, 7.61.

2-(4,5-Bisbenzyloxymethylcyclopent-2-enyl)prop-2-en-1-ol (13).

Sodium borohydride (310 mg, 8.38 mmol) was added to a stirred solution of α,β-unsaturated aldehyde (**12**) (2.0 g, 5.52 mmol) in methanol (100 mL) at ice bath. The mixture was stirred for 3 h at this temperature. Saturated aqueous sodium bicarbonate solution (2 mL) was added to the mixture and then the whole was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 4/1) yielded product (**13**) (1.87 g, 93%) as a viscous oil: IR ($CHCl_3$) 3466, 1792, 1599, 1473 cm^{-1}; EI-MS (70 eV) $C_{24}H_{29}O_3$ m/z (%) = 105 (100), 365 (M^++1, 1); HRMS (ESI, M^++1) calcd for $C_{24}H_{29}O_3$ 365.2117, found 365.2119; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.25 (m, 10H), 5.78 (dt, *J* = 2.5, 5.5 Hz, 1H), 5.64 (dt, *J* = 2.5, 5.5 Hz, 1H), 5.08 (s, 1H), 4.80 (s, 1H), 4.45 (s, 2H), 4.34 (dd, *J* = 11.5, 16.0 Hz, 2H), 4.08 (br s, 2H), 3.57 (dd, *J* = 4.0, 9.5 Hz, 2H), 3.42 (dd, *J* = 9.5, 11.0 Hz, 2H), 3.36 (t, *J* = 9.5 Hz, 1H), 3.15-3.10 (m, 2H), 2.94-2.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.65, 138.20, 137.44, 134.00, 132.04, 128.44 (2x), 128.35 (2x), 128.10 (2x), 127.89, 127.73 (2x), 127.60, 111.74, 73.14, 73.10, 70.38, 67.87, 67.76, 49.84, 48.01, 43.90; Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74; Found: C, 79.22; H, 8.05.

(2-Hydroxymethyl-5-isopropenylcyclopent-3-enyl)methanol (14).

A solution of methanesulfonyl chloride (615 mg, 5.37 mmol) in dichloromethane (1 mL) was added to a stirred solution of compound (**13**) (1.3 g, 3.57 mmol) in pyridine (10 mL) at rt. The reaction mixture was reflux for 2 h. The resulting mixture was washed with brine, cooled to ice bath, poured into aqueous hydrogen chloride solution (2 N, 10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried, filtered and evaporated under reduced pressure to afford crude product. Without further purification, the resulting compound was reacted in the next following step. A three-neck round-bottomed flask (100 mL), equipped with a stirrer, a dropping funnel and a reflux condenser, was filled with liquid ammonia (20 mL), tetrahydrofuran (10 mL) and sodium (530 mg, 23.04 mmol). The resulting residue in tetrahydrofuran (3 mL) was added at -78 °C. The reaction mixture was stirred for 1 h at that temperature. Saturated aqueous sodium bicarbonate solution (2 mL) was added to the mixture and

then the whole was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 1/1) yielded product (**14**) (282 mg, 47%, two-steps from compound **13**) as a viscous oil: IR ($CHCl_3$) 3544, 1421, 1265 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{10}H_{17}O_2$ 169.1229, found 169.1231; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (br s, 2H), 4.90 (s, 1H), 4.75 (s, 1H), 3.79-3.67 (m, 4H), 3.36 (d, *J* = 8.5 Hz, 1H), 3.13-3.09 (m, 1H), 3.00 (br s, 1H), 2.85 (br s, 1H), 2.84-2.78 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.35, 134.03, 131.49, 112.58, 62.66, 61.04, 53.78, 50.62, 44.88, 23.69; Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; Found: C, 71.80; H, 9.88.

7-Benzyloxymethyl-4-methylene-1,3,4,4a,7,7a-hexahydrocyclopenta[*c*]pyran (15).

A solution of methanesulfonyl chloride (103 mg, 0.90 mmol) in dichloromethane (1 mL) was added to a stirred solution of compound (**13**) (300 mg, 0.82 mmol) and sodium iodide (150 mg, 1.00 mmol) in pyridine (5 mL) at rt. The reaction mixture was reflux for 2 h. The resulting mixture was cooled to ice bath, poured into aqueous hydrogen chloride solution (2 N, 10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 4/1) yielded product (**15**) (65 mg, 31%) as a viscous oil: IR ($CHCl_3$) 1630, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.80-5.78 (m, 2H), 4.86 (s, 2H), 4.45 (br s, 2H), 4.05 (d, *J* = 12.5 Hz, 1H), 3.97 (d, *J* = 12.5 Hz, 1H), 3.78 (dd, *J* = 8.5, 12.0 Hz, 1H), 3.61 (dd, *J* = 8.5, 11.5 Hz, 1H), 3.48 (d, *J* = 7.5 Hz, 2H), 3.45-3.42 (m, 1H), 3.08-3.04 (m, 1H), 2.69-2.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.89, 138.27, 133.83, 133.08, 128.37 (2x), 127.70 (2x), 127.60, 110.42, 73.23, 70.91, 69.67, 65.51, 49.01, 48.01, 41.13.

4-Hydroxymethyl-1,1-dimethyl-3,3a,4,6a-tetrahydrocyclopenta[*c*]furan (16).

p-Toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) was added to a solution of compound (**14**) (100 mg, 0.60 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred for 12 h at rt. Saturated aqueous sodium bicarbonate solution (5 mL) was added to the resulting mixture and then the whole was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 1/1) yielded product (**16**) (78 mg, 78%) as a viscous oil: IR ($CHCl_3$) 3548, 1595, 1495, 1352 cm^{-1}; EI-MS (30 eV) $C_{10}H_{16}O_2$ m/z (%) = 79 (100), 168 (M^+, 2); HRMS (ESI, M^++1) calcd for $C_{10}H_{17}O_2$ 169.1229, found 169.1230; ^1H NMR (500 MHz, $CDCl_3$) δ 5.69 (br s, 2H), 3.92 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.86-2.82 (m, 2H), 3.72-3.68 (m, 2H), 3.12-3.06 (m, 2H), 3.01-2.98 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.81, 131.35, 82.38, 65.83, 62.76, 60.59, 50.29, 44.13, 27.31, 24.24.

4-Methanesulfonylmethyl-1,1-dimethyl-3,3a,4,6a-tetrahydrocyclopenta[*c*]furan (17).

A solution of methanesulfonyl chloride (120 mg, 1.05 mmol) in dichloromethane (1 mL) was added to a stirred solution of alcohol (**16**) (70 mg, 0.42 mmol) and pyridine (3 mL) at rt. The reaction mixture was stirred for 2 h at rt. The resulting mixture was cooled to ice bath, poured into aqueous hydrogen chloride solution (2 N, 10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 1/1) yielded product (**17**) (82 mg, 80%) as a viscous oil: IR ($CHCl_3$) 1590, 1174 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{11}H_{19}O_4S$ 247.1004, found 247.1006; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77-5.75 (m, 1H), 5.61-5.60 (m, 1H), 4.30 (dd, *J* = 6.5, 9.5 Hz, 1H), 4.22 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.84 (dd, *J* = 7.0, 10.0 Hz, 1H), 3.75 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.26-3.21 (m, 1H), 3.17-3.10 (m, 2H), 3.03 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.14, 129.97, 81.69, 69.76, 65.51, 61.05, 47.12, 43.76, 37.35, 27.60, 24.32.

4-Methanesulfonylmethyl-1,1-dimethyl-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]furan (18).

A solution of olefin (**17**) (70 mg, 0.28 mmol) in dioxane (2 mL) was added to a solution of 4-toluenesulfonylhydrazine (200 mg, 1.08 mmol) and sodium acetate (100 mg, 1.22 mmol) in the co-solvent of water (5 mL) and l,4-dioxane (5 mL). The reaction mixture was reflux for 4 h. The mixture was cooled to rt, poured into water (5 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 1/1) yielded product (**18**) (53 mg, 75%) as a viscous oil: IR ($CHCl_3$) 1632 cm^{-1}; EI-MS $C_{11}H_{20}O_4S$ m/z (%) = 79 (100), 248 (M^+, 1); HRMS (ESI, M^++1) calcd for $C_{11}H_{21}O_4S$ 249.1161, found 249.1162; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (dd, *J* = 7.0, 10.0 Hz, 1H), 4.20 (t, *J* = 10.0 Hz, 1H), 3.79 (dd, *J* = 8.0, 10.0 Hz, 1H), 3.65 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.01 (s, 3H), 2.99-2.94 (m, 1H), 2.44-2.17 (m, 2H), 1.84-1.78 (m, 1H), 1.77-1.71 (m, 1H), 1.62-1.54 (m, 1H), 1.39-1.31 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.48, 70.92, 65.07, 52.66, 46.01, 42.46, 37.33, 28.67, 28.17, 26.93, 23.65.

1,1-Dimethyl-4-methylene-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]furan (Hop ether) (5).[6c]

A solution of lithium diisopropylamide (1.0 M in tetrahydrofuran, 1.0 mL, 1.0 mmol) was added to a stirred solution of mesylate (**18**) (20 mg, 0.08 mmol) in tetrahydrofuran (10 mL) at -78 °C. The reaction mixture was stirred at reflux for three days. The reaction was quenched with aqueous ammonium chloride solution (15%, 10 mL) and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 8/1) afforded hop ether (**5**) (8 mg, 65%) as a colorless oil: HRMS (EI, M^++1) calcd for $C_{10}H_{17}O$ 153.1280, found 153.1282; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 4.82 (br s, 1H), 4.67 (br s, 1H), 4.07 (dd, *J* = 4.8, 9.0 Hz, 1H), 3.63 (dd, *J* = 4.8, 9.0 Hz, 1H), 3.33-3.25 (m, 1H), 2.39-2.25 (m, 3H), 1.75-1.64 (m, 2H), 1.25 (s, 3H), 1.21 (s, 3H).

6,7-Bisbenzyloxymethyl-2-oxabicyclo[3.2.1]octan-3-one (11).

A solution of ketone (**9**) (2.12 g, 6.06 mmol) in dichloromethane (30 mL) was added dropwise at rt to a stirred solution of *m*-chloroperoxybenzoic acid (1.23 g, 70%, 7.13 mmol) and sodium bicarbonate (2.14 g, 25.48 mmol) in dichloromethane (100 mL). The reaction mixture was stirred at rt for 18 h. The precipitate was filtered through a short plug of Celite and the filtrate was washed with saturated sodium carbonate solution (2 x 20 mL). The organic layer was washed with brine, dried, and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 2/1) yielded lactone (**11**) (1.97 g, 89%) as a viscous oil: IR ($CHCl_3$) 1765, 1167 cm^{-1}; HRMS (EI, M^+) calcd for $C_{23}H_{26}O_4$ 366.1831, found 366.1835; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (m, 10H), 4.84 (br s, 1H), 4.52-4.29 (m, 4H), 3.72-3.39 (m, 4H), 2.72-2.52 (m, 5H), 2.00 (d, *J* = 12.9 Hz, 1H), 1.77 (d, *J* = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.43, 137.88, 137.73, 128.29 (2x), 128.24 (2x), 127.63 (2x), 127.55 (2x), 127.51 (2x), 81.82, 73.36, 73.28, 67.46, 66.81, 45.55, 40.49, 35.18, 34.84, 34.65; Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15; Found: C, 75.47; H, 6.88.

2,3-Bisbenzyloxymethyl-4-(2-hydroxyethyl)cyclopentan-1-ol (19).

Lithium aluminum hydride (350 mg, 9.21 mmol) was added to a stirred solution of lactone (**11**) (2.71 g, 7.40 mmol) in tetrahydrofuran (100 mL) at ice bath. The reaction mixture was further stirred for 3 h at rt. The reaction was quenched with aqueous ammonium chloride solution (15%, 1 mL) and the mixture was concentrated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 2/1) afforded pure diol (**19**) (2.46 g, 90%) as a viscous oil: IR ($CHCl_3$) 3450, 1184 cm^{-1}; HRMS (EI, M^+) calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2145; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 4.52-4.31 (m, 4H), 4.18-4.14 (m, 1H), 3.73-3.45 (m, 6H), 2.45-1.10 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.41, 136.82, 128.62 (2x), 128.37 (2x), 128.23 (2x), 128.03 (2x), 127.97, 127.68, 73.80, 73.33, 72.30, 67.71, 66.79, 62.27, 47.96, 42.93, 42.45, 37.29, 34.28; Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16; Found: C, 74.40; H, 7.98.

7-Methyl-1,3,4,4a,5,6,7,7a-octahydrocyclopenta[*c*]pyran-3,6-dione (21).[8b]

Excess Jones reagent (10 mL) was added to a solution of diol (**19**) (1.53 g, 4.14 mmol) in acetone (50 mL) at rt. The mixture was stirred for 20 min and treated with 2-propanol (4 mL) to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water (10 mL) and

extracted with ether (4 x 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude product. Without further purification, 10% palladium on activated carbon (50 mg) and one drop of 37% hydrogen chloride solution were added to a stirred solution of resulting compound in methanol (20 mL). Hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir for 10 h at rt. The catalyst was filtered through a short plug of Celite and washed with methanol (2 x 20 mL). The combined organic layers were evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 1/1) produced lactone (**21**) (570 mg, 82%, two steps from compound (**19**)) as a solid: mp 86-88 ^{o}C; IR ($CHCl_3$) 1733, 1245 cm^{-1}; HRMS (EI, M^+) calcd for $C_9H_{12}O_3$ 168.0786, found 168.0784; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (dd, *J* = 3.9, 11.7 Hz, 1H), 4.26 (dd, *J* = 4.5, 11.7 Hz, 1H), 2.98-2.76 (m, 2H), 2.61 (dd, *J* = 9.3, 19.2 Hz, 1H), 2.45 (dd, *J* = 6.0, 15.3 Hz, 1H), 2.35-2.27 (m, 2H), 2.20 (dd, *J* = 5.4, 19.2 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.88, 171.69, 68.75, 43.77, 43.29, 40.68, 34.81, 28.04, 13.24; Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19; Found: C, 64.51; H, 7.32.

7-Methyl-1,3,4,4a,5,6,7,7a-octahydrocyclopenta[*c*]pyran-3-one (22).[10j]

1,2-Ethanedithiol (32 mg, 0.34 mmol) was added to ketone (**21**) (50 mg, 0.30 mmol) in dichloromethane (10 mL), and boron trifluoride etherate (0.02 mL) was added to the reaction mixture. The mixture was stirred for 24 h at rt. Saturated aqueous sodium bicarbonate solution (5 mL) was added to the resulting mixture and then the whole was concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to afford crude compound. Purification on silica gel (hexane/ethyl acetate = 4/1) produced dithiane compound (69 mg, 95%) as a solid: mp 120-122 ^{o}C; HRMS (EI, M^+) calcd for $C_{11}H_{16}O_2S_2$ 244.0592, found 244.0587; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (dd, *J* = 3.9, 11.4 Hz, 1H), 4.15 (dd, *J* = 3.9, 11.4 Hz, 1H), 3.35-3.22 (m, 4H), 2.80-2.38 (m, 4H), 2.25-2.14 (m, 1H), 2.12-2.00 (m, 1H), 1.96-1.84 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.76, 74.36, 68.08, 51.49, 46.25, 42.98, 39.60, 39.49, 33.87, 32.26, 13.26; Anal. Calcd for $C_{11}H_{16}O_2S$: C, 54.06; H, 6.60; Found: C, 54.15; H, 6.49.

Raney nickel (100 mg) was added to a stirred solution of dithiane compound (50 mg, 0.2 mmol) in methanol (10 mL) at rt. The reaction mixture was reflux for 24 h. Raney nickel was filtered through a short plug of Celite and washed with methanol (2 x 20 mL). The combined organic layers were evaporated under reduced pressure to afford crude product. Purification on silica gel (hexane/ethyl acetate = 4/1) produced lactone (**22**) (21 mg, 67%) as a solid: mp 56-57 ^{o}C; HRMS (EI, M^+) calcd for $C_9H_{14}O_2$ 154.0994, found 154.0993; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 4.2, 11.4 Hz, 1H), 4.15 (dd, *J* = 4.2, 11.4 Hz, 1H), 2.65-2.55 (m, 2H), 2.39-2.21 (m, 1H), 2.08-1.95 (m, 1H), 1.94-1.68 (m, 3H), 1.33-1.07

(m, 2H), 1.06 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.65, 68.87, 44.85, 37.42, 34.90, 34.86, 34.62, 33.45, 18.73.

ACKNOWLEDGEMENTS

The authors would like to thank the National Science Council (NSC 94-2113-M-390-001) of the Republic of China for financial support.

REFERENCES

1. (a) M. Demuth and K. Schaffiner, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 820. (b) L. F. Tietze, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 828. (c) A. Nangia, G. Prasuna, and P. B. Rao, *Tetrahedron*, 1997, **53**, 14507.
2. (a) U. M. Pagnoni, A. Pinetti, R. Trave, and L. Garanti, *Aust. J. Chem.*, 1976, **29**, 1375. (b) T. Sakan, S. Isoe, S. B. Hyeon, R. Katasumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh, and D. Nelson, *Tetrahedron Lett.*, 1965, 4097.
3. (a) M. Y. Chang, C. H. Lin, A. Y. Lee, H. M. Tai, and N. C. Chang, *J. Chin. Chem. Soc.*, 1999, **46**, 205. (b) A. Y. Lee, M. Y. Chang, H. M. Tai, and N. C. Chang, *J. Chin. Chem. Soc.*, 1999, **46**, 937. (c) A. Y. Lee, M. Y. Chang, and N. C. Chang, *Heterocycles*, 1999, **51**, 295. (d) M. Y. Chang, C. H. Lin, and N. C. Chang, *Tetrahedron*, 2004, **60**, 1581.
4. For isolation of hop ether (a) Y. Naya and M. Kotake, *J. Chem. Soc. Jpn.*, 1967, **88**, 1302. (b) Y. Naya and M. Kotake, *Tetrahedron Lett.*, 1968, 1645.
5. (a) R. Tressl, L. Friese, F. Fendesack, and H. Koeppler, *J. Agric. Food Chem.*, 1978, **26**, 1422. (b) V. E. Peacock and M. L. Deinzer, *J. Am. Soc. Brew. Chem.*, 1981, **39**, 136.
6. For synthesis of hop ether (a) T. Imagawa, N. Murai, T. Akiyama, and M. Kawanisi, *Tetrahedron Lett.*, 1979, **20**, 1691. (b) C. R. Johnson, R. C. Elliott, and N. A. Meanwell, *Tetrahedron Lett.*, 1982, **23**, 5005. (c) D. C. Billington, W. J. Kerr, and P. L. Pauson, *J. Organomet. Chem.*, 1987, **328**, 223. (d) R. J. Linderman and A. Godfrey, *J. Am. Chem. Soc.*, 1988, **110**, 6249. (e) V. V. Veselovsky and A. M. Moiseenkov, *Russ. Chem. Bl.*, 1993, **42**, 102. (f) J. J. Caldwell, I. D. Cameron, S. D. R. Christie, A. M. Hay, C. Johnstone, W. J. Werr, and A. Murray, *Synthesis*, 2005, 3293.
7. (a) For isolation of isoboonein, A. Bianco, A. de Luca, R. A. Mazzei, M. Nicoletti, P. Passacantilli, and R. A. de Lima, *Phytochemistry*, 1994, **35**, 1485. (b) For isolation of boonein, G. B. Marini-Bettolo, M. Nicoletti, I. Messana, M. Patamia, C. Galeffi, J. U. Oguakawa, G. Portalone, and A. Vaciago, *Tetrahedron*, 1983, **39**, 323.
8. For synthesis of isoboonein (a) M. Ohba, T. Haneishi, and T. Fujii, *Chem. Pharm. Bull.*, 1996, **44**, 525. (b) M. Tada, S. Inoue, T. Miki, S.-i. Onogi, J.-i. Kaminaga, J. Hiraoka, Y. Kitano, and K. Chiba, *Chem. Pharm. Bull.*, 1998, **46**, 1451.

9. For isolation of iridomyrmecin, R. Fuson, R. Trave, and A. Vercellon, *Chim. Ind.* (Milan), 1955, **37**, 251.

10. For synthesis of iridomyrmecin (a) S. Brechbuhler-Bader, C. J. Coscia, P. Loew, C. von Szczepanski, and D. Arigoni, *J. Chem. Soc., Chem. Commun.*, 1968, 136. (b) P. A. Grieco and C. V. Srinivasan, *J. Org. Chem.*, 1981, **46**, 2591. (c) P. Callant, R. Ongena, and M. Vandewalle, *Tetrahedron*, 1981, **37**, 2085. (d) T. F. Wang and C. F. Yang, *J. Chem. Soc., Chem. Commun.*, 1989, 1876. (e) D. Friedrich and L. A. Paquette, *J. Org. Chem.*, 1991, **56**, 3831. (f) J. M. Takacs and Y. C. Myoung, *Tetrahedron Lett.*, 1992, **33**, 317. (g) M. Kigawa, M. Tanaka, H. Mitsuhashi, and T. Wakamatsu, *Heterocycles*, 1992, **33**, 117. (h) G. Nangia, G. Prasuna, and P. B. Rao, *Tetrahedron Lett.*, 1994, **35**, 3755. (i) G. Nangia and G. Prasuna, *Tetrahedron*, 1996, **52**, 3435. (j) D. M. Hodgson, A. R. Gibbs, and M. G. B. Drew, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3579. (k) G. Zanoni, F. Agnelli, A. Meriggi, and G. Vidari, *Tetrahedron Asymm.*, 2001, **12**, 1779. (l) M. Ernst and G. Helmchen, *Synthesis*, 2002, 1953. (m) D. E. Chavez and E. N. Jacobsen, *Org. Lett.*, 2003, **5**, 2563. (n) D. M. Hodgson and A. R. Gibbs, *Synlett*, 1997, 657. (o) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, 1959, 217. (p) J. Falbe, H. Weitkamp, and F. Korte, *Tetrahedron*, 1963, **19**, 1479.

11. (a) T. Matsui, *Tetrahedron Lett.*, 1967, 3761. (b) J. Meinwald and R. A. Schneider, *J. Am. Chem. Soc.*, 1965, **87**, 5218.

12. For other reports of iridoid synthesis starting from bicyclo[2.2.1]heptanes. (a) R. C. Kelly and I. Schletter, *J. Am. Chem. Soc.*, 1973, **95**, 7156. (b) K. Furuchi, K. Abe, and T. Miwa, *Tetrahedron Lett.*, 1974, 3685. (c) Y. Arai, S. Kawanami, and T. Koizumi, *Chem. Lett.*, 1990, 1585. (d) I. Fleming and N. K. Terrett, *Tetrahedron Lett.*, 1984, **25**, 5103. (e) P. Callant, P. Storme, E. van der Eycken, and M. Vandewalle, *Tetrahedron Lett.*, 1983, **24**, 5797.

13. Y. S. Hon, F. J. Chang, L. Lu, and W. C. Lin, *Tetrahedron*, 1998, **54**, 5233.