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Stereocontrolled Total Synthesis of (±)-Culmorin via the Intramolecular Double Michael Addition

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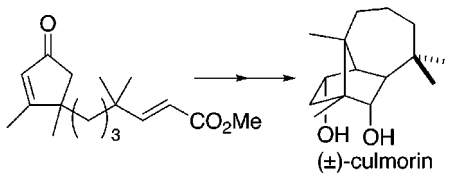
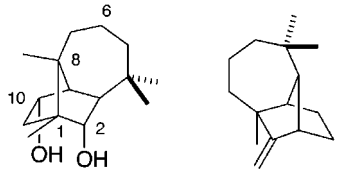
ABSTRACT



We have accomplished the total synthesis of (±)-culmorin from the readily available ketone (11 steps, 46% overall yield). The tricyclo[6.3.0.0^{3,9}]-undecan-10-one skeleton, the culmorin framework, was constructed via the intramolecular double Michael addition of the cyclopentenone having an α,β-unsaturated ester moiety by using LHMDS. The stereochemistry of newly generated four stereogenic centers was perfectly controlled by the reaction.

(−)-Culmorin (**1**, Chart 1) is a sesquiterpene isolated from *Fusarium culmorum* as a mold metabolite by Ashley et al. in 1937[1] and its structure was determined by Barton and coworkers in 1968.[2] Culmorin has antifungal activity against a variety of fungi, especially ones in wheat and corn.[3] The total synthesis of culmorin was reported by Roberts' group in 1969.[4] They utilized the Dieckman condensation twice to form a tricyclo[6.3.0.0^{3,9}]undecane framework, and therefore, the chemical yield and the stereoselectivity were quite low. Additionally, Nayak et al. reported the partial synthesis of (+)-culmorin from naturally occurring (+)-longifolene (**2**),[5] which has the same ring system as culmorin, in 10 steps with low yield.[6] Recently, we have reported highly stereoselective constructions of the tricyclo[5.3.0.0^{3,8}]decane and tricyclo[6.3.0.0^{3,9}]undecane frameworks[7] utilizing the intramolecular double Michael addition[8,9] under several conditions. This strategy has advantages on the basis of the

Chart 1



(+)-culmorin[a] (**1**) (+)-longifolene (**2**)

[a] The antipode of natural (−)-culmorin is shown.

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(1) Ashley, J. N.; Hobbs, B. C.; Raistrick, H. *Biochem. J.* **1937**, *31*, 385−397.

(2) (a) Barton, D. H. R.; Werstiuk, N. H. *Chem. Commun.* **1967**, 30−31; (b) *J. Chem. Soc. C* **1968**, 148−155.

(3) (a) Strongman, D. B.; Miller, J. D.; Calhoun, L.; Findlay, J. A.; Whitney, N. *J. Bot. Mar.* **1987**, *30*, 21−26. (b) Wang, Y. Z.; Miller, J. D. *Phytopath. Z.* **1988**, *122*, 118−125. (c) König, G. M.; Wright, A. D. *Planta Med.* **1996**, *62*, 193-211.

(4) Roberts, B. W.; Poonian, M. S.; Welch, S. C. *J. Am. Chem. Soc.* **1969**, *91*, 3400−3401.

(5) (a) Review: Dev, S. *Acc. Chem. Res.* **1981**, *14*, 82−88. (b) Simonsen, J. L. *J. Chem. Soc.* **1920**, *117*, 570−578.

(6) Reddy, R. T.; Nayak, U. R. *Indian J. Chem.* **1986**, *25B*, 457−461.

(7) Ihara, M.; Makita, K.; Fujiwara, Y.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 6416−6421.

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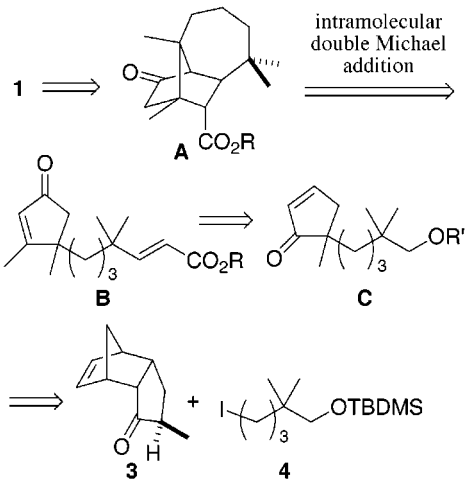
following reasons. First, the tricyclo system could be built in a single operation. Second, several protective and deprotective processes could be omitted. Finally, the stereo- and regioselectivities could be highly controlled. Herein, we report an efficient synthesis of (±)-culmorin by the application of this methodology.

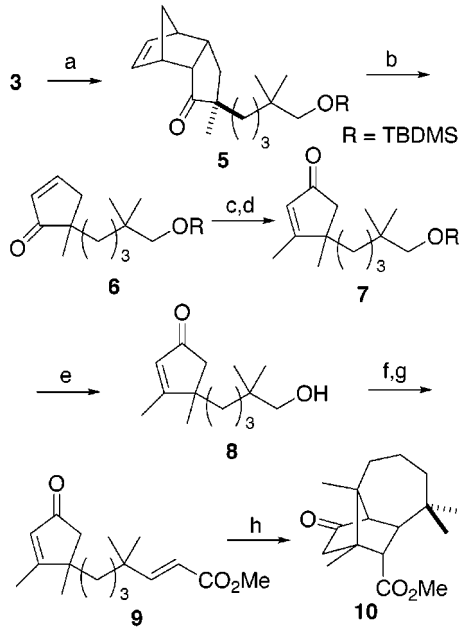
The retrosynthetic analysis for (±)-**1** using the intramolecular double Michael addition as the key step is shown in Scheme 1. **1** would be derived through stereoselective reduction of the ketone and oxidative decarboxylation from the tricyclo[6.3.0.0^{3,9}]undecan-10-one derivative **A**. **A** could be obtained by the intramolecular double Michael addition of the α,β-unsaturated ester **B**, which can be transformed from the cyclopentenone **C**. α-Alkylation of the known ketone **3** with the iodide **4**, which corresponds to the side chain moiety, would afford **C**.

Scheme 1. Retrosynthetic Analysis of (±)-Clumorin (**1**)



The construction of the tricyclo[6.3.0.0^{3,9}]undecan-10-one derivative **10**, which has the culmorin framework, is depicted in Scheme 2. Thus, **5** was obtained by α-alkylation of **3**[10] using the iodide **4**[11] and then transformed into **6** by pyrolysis. After 1,2-addition of MeLi to the enone **6**, the corresponding allyl alcohol was oxidized by PCC in the presence of 4 Å molecular sieves to give the O-migrated enone **7**. After its deprotection, oxidation of **8** with PCC in the presence of 4 Å molecular sieves, followed by the Horner−Wadsworth−Emmons olefination, afforded the (*E*)-α,β-unsaturated ester **9** as the key substrate.

Scheme 2. Construction of the Culmorin Skeleton



a) $NaCH_2S(O)CH_3$, **4** (94%); b) Ph_2O, 250 °C (84%); c) MeLi; d) PCC, molecular sievs 4Å (87% for **2** steps); e) TBAF (98%); f) PCC, molecular sievs 4Å; g) $(MeO)_2P(O)CH_2CO_2Me$, NaH (88% for **2** steps); h) LHMDS, −78 to 0 °C (94%)

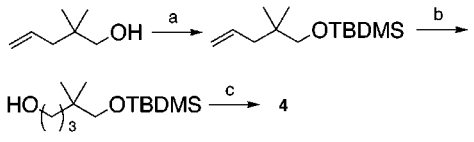
The intramolecular double Michael addition of **9** was examined under four representative methods A−D: (A) LHMDS,[8b] (B) TMSI−HMDS,[7,12,13] (C) Bu_2BOTf-HMDS,[7,14] and (D) TMSCl−NEt_3−ZnX_2.[7,15] Method A, carried out with LHMDS at −78 to 0 °C, gave the expected compound **10** as the sole stereoisomer in a very high yield (94% yield).[16] The same product **10** was obtained in 39% yield by the treatment of **9** with TMSCl−NEt_3−$ZnBr_2$ at a refluxing temperature (method D). The stereochemistry of **10** was confirmed on the basis of the long-range coupling (J = 1.8 Hz) between the C(2) and C(11) equatorial hydrogens derived from the W-shaped configuration in the ^{1}H NMR spectrum. On the other hand, neither method B nor C gave the desired compound **10** (only produced complicated adducts as in-

(8) (a) Review: Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010−1022. (b) Ihara, M.; Makita, K.; Tokunaga, Y. Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 6008−6013 and reference therein.

(9) Recent efforts of intermolecular version: (a) Nagaoka, H.; Shibuya, K.; Kobayashi, K.; Miura, I.; Muramatsu, M.; Yamada, Y. *Tetrahedron Lett.* **1993**, *34*, 4039−4042. (b) Maiti, S.; Bhaduri, S.; Achari, B.; Banerjee, A. K.; Nayak, N. P.; Mukherjee, A. K. *Tetrahedron Lett.* **1996**, *37*, 8061−8062. (c) Hagiwara, H.; Yamada, Y.; Sakai, H.; Suzuki, T.; Ando, M. *Tetrahedron* **1998**, *54*, 10999−11010.

(10) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982−5984.

(11) The side chain moiety **4** was synthesized, as follows, from the readily available alcohol[20] in four steps.



a) TBDMSCl, NEt_3, DMAP (93%); b) BH_3•THF; NaOH, H_2O_2 (95%); c) PPh_3, I_2, imidazole (92%)

(12) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730−732.

(13) (a) Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1993**, *115*, 8107−8115. (b) Ihara, M.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 8092−8100.

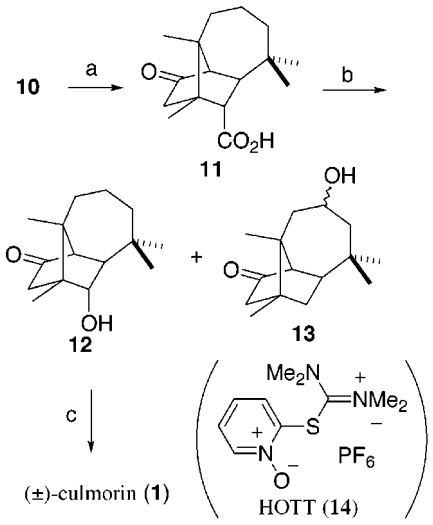
(14) Ihara, M.; Taniguchi, T.; Yamada, M.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *34*, 8071−8074.

(15) (a) Ihara, M.; Makita, K.; Takasu, K. *J. Org. Chem.* **1999**, *64*, 1259−1264. (b) Snowden, R. L.; *Tetrahedron Lett.* **1981**, *22*, 97−100; (c) *Tetrahedron* **1986**, *42*, 3277−3290.

separable mixtures). The complete stereoselectivity under these conditions can be explained by a chelated transition state. The chelation among one oxygen of the ester group, another oxygen of the enolate derived from the enone, and the countercation should fix the conformation of the transition state.

The total synthesis of culmorin was accomplished as follows (Scheme 3). Hydrolysis of **10** quantitatively gave

Scheme 3. Total Synthesis of (±)-Culmorin (**1**)



a) KOH (>99%); b) HOTT (**14**), NEt_3, DMAP, 1,4-dioxane; *t*-BuSH, O_2, 80 °C; $P(OMe)_3$ (82% for **12**, 8% for **13**); c) Li, NH_3, MeOH, −78 °C (>99%)

11. Conversion of the carboxylic group into the hydroxyl function at the C(2) position of **11** was performed by Barton's oxidative decarboxylation method. A typical Barton procedure[17] utilizing 2-mercaptopyridine *N*-oxide gave the desired alcohol **12** in 48% yield as the sole stereoisomer. Recently, Garner and co-workers reported an improved Barton's method employing *S*-(1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT, **14**).[18] We applied this method to the oxidative decarboxylation of **11** under an O_2 current. When the reaction was carried out in THF−benzene, the desired alcohol **12** and the regioisomeric alcohols **13**[6] were obtained in 38 and 10% yields, respectively. However, when 1,4-dioxane was employed as the solvent, the yield of **12** increased to 82% yield and **13** was provided in 8% yield.[19] The stereochemistry of **12** was characterized by ^{1}H NMR, which also exhibited long-range coupling (J = 1.6 Hz) between the hydrogens at C(2) and C(11). The generation of byproduct **13** could be explained by the [1,5]-hydrogen shift (C(6) to C(2)) of the radical intermediate, followed by reaction with an O_2 molecule.

Barton and co-workers have briefly mentioned the reduction of **12** to **1** with Na and *i*-PrOH; however, its yield was quite low (ca.14% yield) and the stereoselectivity at the C(10) position was not described.[2b] We achieved an improvement in this transformation. Thus, Birch reduction at low temperature quantitatively gave only the desired stereoisomer **1**. Spectral data of the synthetic compound **1** were very consistent with those reported.[2]

In conclusion, the application of the intramolecular double Michael addition of cyclopentenones having an α,β-unsaturated ester moiety permits the rapid assembly of the tricyclo[6.3.0.0^{3,9}]undecan-10-one system with complete stereoselectivity. We have thus achieved the total synthesis of (±)-culmorin from the known ketone **3** (11 steps, 46% overall yield!).

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(16) **Procedure of the Intramolecular Double Michael Reaction of 9 under Condition A.** To a solution of HMDS (1.16 mL, 5.52 mmol) in Et_2O (45 mL) at 0 °C was added BuLi (1.54 M in hexane, 2.69 mL, 4.14 mmol). The solution was stirred at 0 °C for 1 h and then cooled to −78 °C. To this was added a solution of **9** (768 mg, 2.76 mmol) in Et_2O (3 mL) dropwise at −78 °C. The resulting mixture was stirred for 1 h at −78 °C and for an additional 3 h at 0 °C. After dilution with Et_2O, the mixture was washed with 10% HCl and brine. The organic layer was dried and concentrated. Column chromatography on silica gel (AcOEt/hexane = 1:9 v/v) and recrystallization from *i*-Pr_2O afforded **10** (724 mg, 94%) as colorless needles: mp 150 °C; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 2.76 (dd, 1H, J = 6.9, 1.8 Hz), 2.46 (s, 1H), 2.26 (d, 1H, J = 17.8 Hz), 2.04 (d, 1H, J = 6.9 Hz), 1.94 (ddd, 1H, J = 17.8, 1.8, 0.8 Hz), 1.60−1.35 (m, 6H), 1.10 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.78 (s, 3H); IR ($CHCl_3$) ν 1735 cm^{-1}; MS (EI) 278 (M^+). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.26; H, 9.42.

(17) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.

(18) Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem.* **1998**, *63*, 5732−5733.

(19) **Procedure of the Oxidative Decarboxylation Reaction of 11 Using HOTT (14)**. To a mixture of HOTT[18] (**14**; 171 mg, 0.46 mmol) and DMAP (2.8 mg, 23 μmol) was added a solution of **11** (61 mg, 0.23 mmol) and NEt_3 (0.13 mL, 0.92 mmol) in 1,4-dioxane (2.5 mL), which was stirred for 12 h at room temperature under an Ar atmosphere. After the addition of *t*-BuSH (0.23 mL, 2.1 mmol), the mixture was stirred for 3 h at 80 °C under an O_2 current. To this was added $P(OMe)_3$ (0.27 mL, 2.3 mmol) at room temperature, and the resulting mixture was stirred for a further 2 h at room temperature. After the addition of saturated NH_4Cl, the mixture was extracted with Et_2O. The organic layer was then dried and concentrated. Column chromatography on silica gel (AcOEt/hexane = 1:4 v/v) afforded **13**[6] (4.3 mg, 8%) as a colorless solid and a crude product of **12**. The crude product was further purified by column chromatography on silica gel (Et_2O/benzene = 1:4 v/v) and then recryctallized from cyclohexane−petroleum ether to give **12** (44.6 mg, 82%) as colorless needles: mp 129−132 °C; ^{1}H NMR ($CDCl_3$) δ 4.06 (dd, 1H, J = 4.7, 1.6 Hz), 2.62 (d, 1H, J = 18.4 Hz), 2.37 (s, 1H), 1.85 (dt, 1H, J = 18.4, 1.6 Hz), 1.65 (br s, 1H), 1.58−1.37 (m, 6H), 1.27 (d, 1H, J = 4.7 Hz), 1.04 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H); IR ($CHCl_3$) ν 3600, 3450, 1735 cm^{-1}; HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1812.

(20) Pattenden, G.; Teague, S. J. *Tetrahedron* **1987**, *43*, 5637−5652.