Enhancive Synthesis of (±)-1β,11-Diol-4-en-eudesmol†

CHEN, Jin-Chun(陈锦春) ZHENG, Guo-Jun(郑国君) ZHANG, Chen(张琛)
FANG, Li-Jing(房丽晶) LI, Yu-Lin*(李裕林)
National Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, China

An enhancive synthesis of (±)-1β, 11-diol-4-en-eudesmol, starting from 2-chloroacrylonitrile, is described. The effect of temperature on the Diels-Alder reaction of 2-chloroacrylonitrile with 2-methylfuran and the condition of cationic cyclization of diene were discussed in detail.

Keywords Diels-Alder reaction, cationic cyclization, eudesmane, sesquiterpenoids

Introduction

In eudesmane family, a large number of compounds have an oxygenated functional group at C_1.[1] Although considerable efforts have been devoted to the total synthesis of eudesmane type of sesquiterpenoids natural products and some germacrane sesquiterpenoids starting from the corresponding eudesmane over the past decades, the introduction of C_1 oxygenated functional group still represents significant challenge.[2] Recently, our group found a novel general and diversified strategy.[3] There are two problems, the starting material and the yield of the cationic cyclization, in the case that it is applied in the total synthesis of complex natural products. Here some progresses about them in our laboratory were reported.

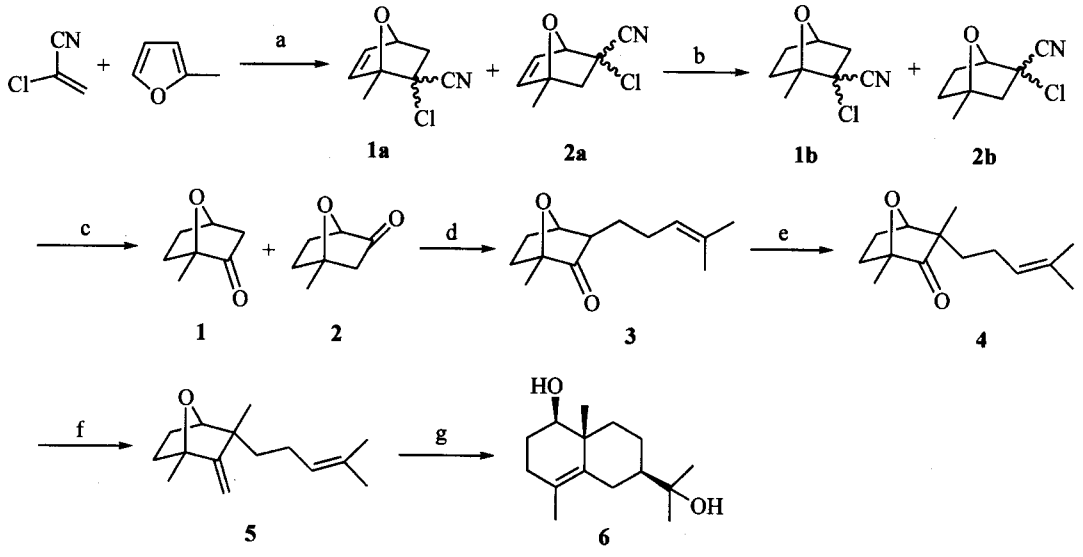
Results and discussion

1-Methyl-7-oxabicyclo[2.2.1]heptan-2-one (**1**) is a very useful starting material in the synthesis of the C_1-oxygenated eudesmane and some natural products with the 1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptan system, such as (±)-3′,6′-epoxycycloaurapten, (±)-2,5-epoxymegastigma-6(*E*),8(*E*)-diene and its 6(*Z*) isomer.[4,5] It has been reported that the reaction of 2-methylfuran with 2-chloroacrylonitrile gave a mixture of regio- and stereoisomers (**1a** + **2a**) in 62% yield after four weeks at 4 ℃ or in 79% yield after a month at 0 ℃.[4,6] However, attempts to repeat these experiments led to low yields (20% and 65%) in ratio of 3∶1 (**1a**/**2a**). In our current investigation on the synthesis of natural eudesmane and argarofuran type of sesqueterpeniods, the high purity of compound **1** was necessary. Kinds of conditions have been studied in order to improve the ratio and yields of **1a** and **2a**. First, our group presumed that the cause was the slight amount of water present in reaction mixture.[3] But in further study, it was found that the temperature instead of water intensively influenced this intermolecular Diels-Alder reaction and zinc iodide was the best catalyst. When the reaction underwent under argon at −20 ℃, the ratio of **1a** and **2a** could reach up to 10∶1 (determined mainly by ^{1}H NMR), the yield was higher than that reported in literature,[4,6] and the reaction time was shortened to a week. Because **1a** and **2a** were particularly unstable at room temperature, it was ease to go on a reverse Diels-Alder reaction to the starting materials. So the product was immediately hydrogenated to remove 5,6 double bond, and the saturated adducts **1b** and **2b** were obtained in 91% overall yield (Scheme 1). After they were hydrolysied to the ketones,[7] the ^{1}H NMR spectrum of the product showed that the purity exceeded 95%, and the ratio of **1** and **2** exceeded 20∶1 by GC determination. During the experiment, it was found that the water layer contained large amount of ketones. The yield reported in literature may be too high and the disposal method should be changed (Authors hope to discuss this problem with Prof. Albert T. Sneden, Virginia Commonwealth University, U.S.A[4]).

By the reported method (Scheme 2),[3] compound **1** was first alkylated with homoprenyl iodide (LHMDS, −78 ℃ to r.t.) to give oxabicyclic ketone **3** in 65% isolated yield. The product was then alkylated with methyl iodide to give compound **4** (LDA, −78 ℃ to r.t.). Following a Wittig reaction, the cyclization precursor **5** was obtained in 85% yield. Interestingly, when diene **5** was treated with a variety of Lewis acids such as $TiCl_4$, $SnCl_4$, $BF_3\cdot Et_2O$, MgI_2 and so on under the variety of reaction conditions (temperature and solvent), it was decomposed and the unidentified products were afforded only in low yield.

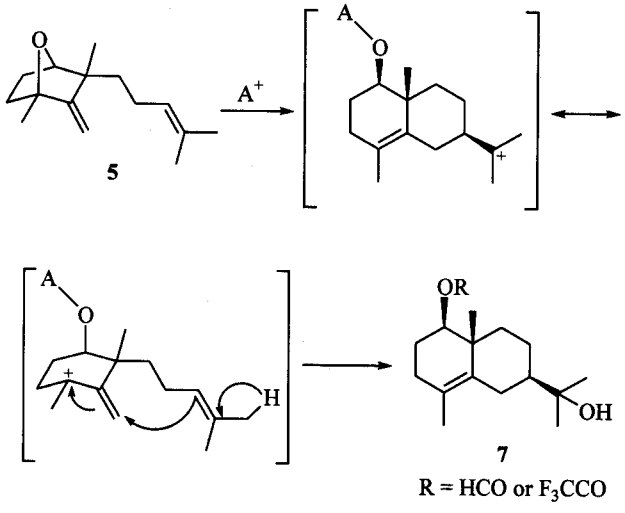
* E-mail: liyl@lzu.edu.cn
Received January 7, 2003; revised February 25, 2003; accepted April 10, 2003.
Project supported by the National Natural Science Foundation of China (No. 20272021).
†Dedicated to Professor ZHOU Wei-Shan on the occasion of his 80th birthday.

Scheme 1



Reagents and conditions: (a) ZnI_2, −20 ℃, a week; (b) 10% Pd-C/H_2, EtOAc, 12 h; (c) KOH, *t*-BuOH/H_2O, reflux 10 h; (d) LHMDS/homoprenyl iodide, −78 ℃, 3 h; (e) LDA/methyl iodide, −78 ℃, 2 h; (f) $(Ph_3)P=CH_2$/THF r.t., 12 h; (g) 85% TFA/acetone, reflux 6 h.

Scheme 2



When it was treated with 99% formic acid or 98% trifluoroacetic acid, the reaction was very complex and the corresponding ester of compound **6** could be obtained in very low yield (< 5%). No reaction occurred while treating with 50% formic acid or trifluoroacetic acid. When 88% formic acid or 85% trifluoroacetic acid was used at room temperature, the corresponding ester was isolated in less than 15% yield and the repetition was worse.[3] Thus, it was considered that the concentration of the acids strongly influenced this electrophilic olefin cyclization of tetrahydrofuran diene **5**. Fortunately, when 85% TFA was diluted with acetone (*V*/*V*, 1:5), only two spots were shown in TLC and eudesmol (**6**)[8] was gained in higher yield (35%) after refluxing for 6 h. Other compounds could not be identified (Scheme 1). Under this condition, the repetition of yield was very stable (±5%).

In summary, two more relative rational conditions are found. The results are very useful in enhancive synthesis of 1-methyl-7-oxabicyclo[2.2.1]heptan-2-one (**1**), a precursor which was used in synthesis of some natural products and in the cationic cyclization, a key step which was used in synthesis of C_1 oxygenated decalin ring type of sesquiterpenoids. Application of these two methods to synthesis a number of naturally polyhydroxylated agarofuran and complex C_1-oxygenated eudesmane is under active investigation.

Experimental

For flash column chromatography, silica gel (200—300 mesh), light petroleum ether (b.p. 30—60 ℃), ethyl ether and *n*-pentane were used. IR spectra were recorded on an Nicolet AVATAR 360 FT-IR spectrometer as liquid films. ^1H NMR and ^{13}C NMR spectra were taken on a Bruker AM-400 spectrometer with TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were determined on VG ZAB-HS and Bruker APEXII 47e spectrometers.

1-*Methyl*-7-*oxabicyclo*[2.2.1]*heptan*-2-*one* (**1**)

To a stirred flask, containing zinc iodide (2.0 g, 6.28 mmol) and 2-chloroacrylonitrile (15.84 g, 181 mmol), 2-methyfuran (16.53 g, 201.3 mmol) was added by dropwise at 0 ℃ under argon. The yellow solution was stirred for another 10 min and then placed in a refrigerator kept at −20 ℃ for a week in the absence of light. The mixture was diluted with ethyl ether (200 mL), washed with 7% $NaHCO_3$ (3 × 50 mL), saturated NaCl (30

mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the white solid of **1a + 2a** (29 g, 94%, m.p. 4 ℃). The isomeric mixture (35.64 g, 210 mmol) was dissolved in ethyl acetate (100 mL), filtered to remove any residual zinc iodide, and 10% Pd-C catalyst (2.15 g) was added to the solution. The mixture was hydrogenated for 12 h. The Pd catalyst was removed by filtration through celite and the filtrate was concentrated under reduced pressure to give the slight yellow oil. After distillation, a mixture of **1b + 2b** (in ratio of 10:1, determined by ^1H NMR) was obtained as colorless oil, 35.06 g (91%, from 2-chloroacrylonitrile). ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.48—1.70 (m, 2H), 1.63 (s, 3H), 1.87—1.94 (m, 1H), 2.01 (d, J = 13.8 Hz, 1H), 2.41—2.48 (m, 1H), 2.81—2.86 (m, 1H), 4.56 (t, J = 4.5 Hz, 1H); EIMS m/z (%): 173 (1.4, M^+), 171 (4.8, M^+), 144 (1.2), 142 (3), 136 (7.8), 108 (14.8), 84 (44), 58 (38), 43 (100), 39 (20).

A solution of **1b + 2b** (25.4 g, 148 mmol) in THF (20 mL) was added dropwise to a stirred solution of KOH (21.26 g, 380 mmol) in *t*-BuOH (100 mL) and water (12 mL) at 50 ℃ over 1 h. The dark solution was stirred for an additional 0.5 h at 50 ℃ and then heated to reflux for 10 h with vigorous stirring. The burgundy-colored solution was cooled to r.t. and diluted with light petroleum ether (300 mL). The mixture was washed with 5% $NaHCO_3$ (3 × 50 mL) and water (5 × 100 mL), and the water layer was extracted with light petroleum ether (8 × 150 mL). The combined organic layer was washed with water (3 × 100 mL), saturated NaCl (30 mL), and dried over anhydrous $MgSO_4$. After evaporating of the solvent by rectification, the residue was purified by silica gel chromatography. The washing solution (*n*-pentane/ethyl ether, 10:1) was removed by rectification, and **1** was afforded as colorless liquid, 12.12 g (65 %). ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 3H, 1-Me), 1.64—1.75 (m, 3H, 5-αH, 6-H_2), 2.06—2.09 (m, 1H, 5-βH), 2.11 (d, J = 17.4 Hz, 1H, 3-αH), 2.52 (ddd, J = 17.3, 5.9, 2.7 Hz, 1H, 3-βH), 4.79 (t, J = 5.7 Hz, 1H, 4-H); MS (EI) m/z (%) 126 (7, M^+), 98 (100), 83 (32), 71 (6), 55 (27). Anal. calcd for $C_7H_{10}O_2$: C 66.65, H 7.99; found C 66.37, H 8.21.

(±)-1β,11-*Diol*-4-*en*-*eudesmol* (**6**)

To a 25-mL flask, the 1,4-diene **5** (220 mg, 1.0 mmol), prepared by the reported method,[3] acetone (10 mL) and 85% trifluoroacetic acid (2 mL) were added. The mixture was heated to reflux under argon. After 6 h, the reaction solution was cooled to 0 ℃ and 3 mol/L NaOH (10 mL) was added dropwise. The resulting mixture was allowed to room temperature and stirred for half an hour. The acetone was removed under reduced pressure and the remains were extracted with ether (3 × 60 mL). The combined organic layers were washed with water, brine, respectively, and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography to yield eudesmol **6** (95 mg, 40% yield) as white needles. m.p. 151—153 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.02 (s, 3H), 1.22 (s, 6H), 1.16—1.17 (m, 2H), 1.60 (brs, 3H), 1.67—1.73 (m, 4H), 1.97—2.18 (m, 4H), 2.63 (dt, J = 13.9, 2.6 Hz, 1H), 3.44—3.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.3, 19.0, 26.5, 26.7, 27.1, 27.2, 31.9, 38.9, 39.5, 49.8, 72.7, 78.4, 123.9, 133.6; HRMS (ESI): calcd for $C_{15}H_{26}O_2Na$ [M + Na^+] 261.1825, found 261.1828.

References

1 For reviews of natural sesquiterpenes to see:
Fraga, B. M. *Nat. Prod. Rep.* Each year from **1983** to **2002** and references cited there in.

2 (a) Wharton, P. S.; Sundin, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34.
(b) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1994**, *50*, 4755.
(c) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
(d) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941.
(e) Boyer, F. D.; Ducrot, P. H. *Synthesis* **2000**, *13*, 1868.
(f) Moreno-Dorado, F. J.; Guerra, F. M.; Aladro, F. J.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron* **1999**, *55*, 6997.

3 Zhang, Z.; Li, W. D.; Li, Y. L. *Org. Lett.* **2001**, *3*, 2555.

4 Difazio, P. M.; Wallace, W. A.; Sneden, A. T. *Heterocycles* **1989**, *29*, 2391.

5 Difazio, P. M.; Sneden, A. T. *J. Nat. Prod.* **1990**, *53*, 1357.

6 Schuda, P. F.; Bennet, J. M. *Tetrahedron Lett.* **1982**, *23*, 5525.

7 Shiner, C. S.; Fisher, A. M.; Yacoby, F. *Tetrahedron Lett.* **1983**, *24*, 5687.

8 Su, W. C.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *39*, 603.

(E0301073 SONG, J. P.; DONG, H. Z.)