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Total synthesis of (−)-mniopetal E, a novel biologically intriguing drimane sesquiterpenoid †

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Abstract

Total synthesis of (−)-mniopetal E, the common skeleton of the biologically intriguing mniopetals A–D, was accomplished for the first time. The key step of the total synthesis was stereoselective intramolecular Diels–Alder reaction for construction of the octahydronaphthalene core structure. Our total synthesis as natural enantiomeric form established the unsettled absolute stereochemistry of the antibiotic. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: biologically active compounds; Diels–Alder reactions; terpenoids.

Mniopetals A–E (**1–5**) are novel drimane-type sesquiterpenoids, which were isolated from the fermentation broth of *Mniopetalum* sp. 87256.[1] These natural products show inhibitory activity against RNA-directed DNA-polymerases (RT) of human immunodeficiency virus (HIV)-1 and moloney murine leukemia viruses.[1] In addition, they exhibit antimicrobial and cytotoxic properties to some extent.[1] Their structures, highly oxygenated octahydronaphthalenes, were elucidated by a combination of chemical and spectroscopic methods (Fig. 1)[2]. Their absolute stereochemistries were proposed as depicted based on the correlation with the stereochemically defined 1α,15-dihydroxymarasmene (**6**)[3,4] isolated from the same fungus. In this communication, we report the first total synthesis of mniopetal E (**5**), which is the common structure of all the mniopetal family.

In our previous paper,[5] the intermediate **8** derived from a D-ribitol derivative **7** was converted to the substrate **9** for the key intramolecular Diels–Alder (IMDA) reaction,[6] in which a γ-butenolide part was installed as a dienophile (Scheme 1). The IMDA reaction of **9** proceeded under thermal conditions to provide two *endo*-adducts **10** (54%) and **11** (22%) with preferential formation of the desired **10**. Unfortunately, we could not find any efficient synthetic route from **10** to mniopetal E (**5**).[7]

We prepared another substrate **15** for the IMDA reaction as illustrated in Scheme 2. The ester **8** was converted to unsaturated aldehyde **12**[8] by a reduction–oxidation procedure. Protection of the aldehyde

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† This paper is dedicated with respect and admiration to Professor Kenneth L. Rinehart on the occasion of his 70th birthday.

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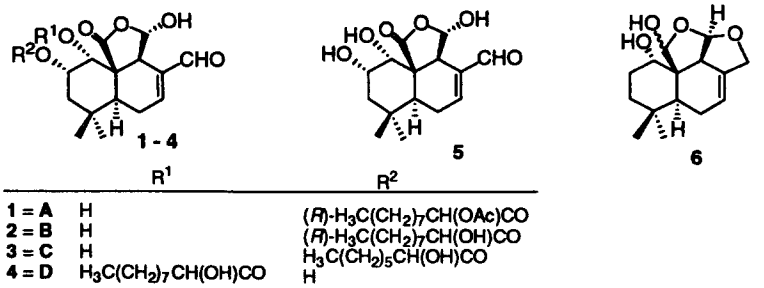
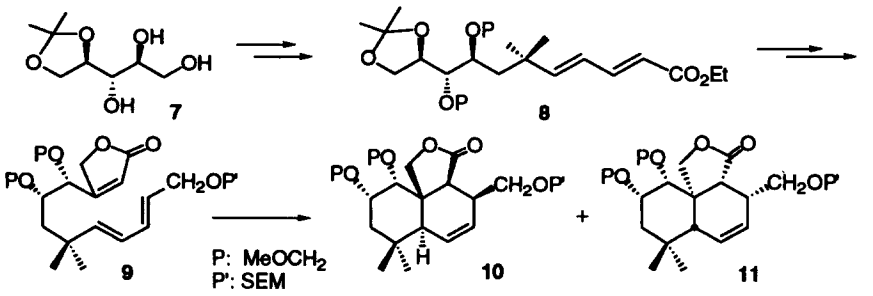
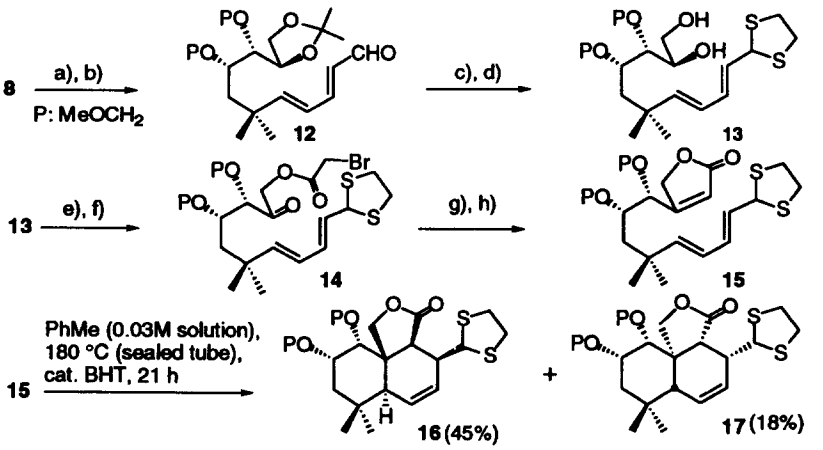


Figure 1.



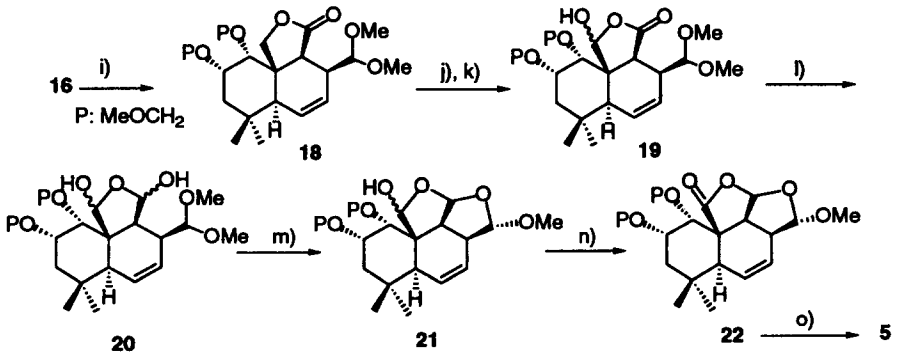
Scheme 1.

group in **12** as the 1,3-dithiolane and hydrolysis of the ketal provided diol **13**. Introduction of a γ-butenolide moiety was achieved using the previously established strategy.[5] Thus, **13** was converted to the α-bromoacetylmethyl ketone **14**, which was treated with trimethylphosphite. The resulting α-phosphonoacetate was subjected to an intramolecular Horner–Emmons reaction providing **15** in an overall yield of 35% from **13**. The IMDA reaction of **15** proceeded in toluene (0.03 M solution) at 180°C for 21 h. As a result, two *endo*-adducts **16** and **17** were obtained in 45% and 18% yields, respectively. The stereochemical assignment of **16** and **17** as depicted was conducted based on their ^{1}H NMR spectral analysis including NOE experiments. We consider that the same transition state argument as described in the case of **9**[5] can be adopted for explanation of the present stereochemical outcome.



Scheme 2. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78°C; (b) MnO_2, CH_2Cl_2; (c) $HS(CH_2)_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −18°C; (d) AcOH:H_2O:THF (3:1:1) (90% from **8**); (e) $ClC(O)CH_2Br$, γ-collidine, CH_2Cl_2, −78°C; (f) DMSO, TFAA, Et_3N, CH_2Cl_2, −50°C; (g) $P(OMe)_3$ (neat), 90°C; (h) LiCl, DIPEA, MeCN (35% from **13**)

The transformation of the major adduct **16** into mniopetal E (**5**) was depicted in Scheme 3. All attempts to convert the γ-butyrolactone moiety in **16** directly to a succinic anhydride or a γ-hydroxy-γ-lactone structure failed. Thus, the dithiolane part in **16** was temporarily converted to the dimethyl acetal group.[9] The γ-lactone ring in the resulting acetal **18** was hydrolyzed to afford the ring opened carboxylic acid, in which the primary hydroxyl group was oxidized to an aldehyde isolating as a diastereomeric mixture **19** of the γ-hydroxy-γ-lactones. Reduction of **19** with DIBAL-H provided **20**. Treatment of **20** with HCl gave tetracyclic methyl acetal **21**. The hemiacetal moiety of **21** was then oxidized to lactone **22**[10] and successive treatment with HCl finally provided (−)-mniopetal E (**5**)[10] as a consequence of hydrolysis of the protecting groups and double bond migration. The spectroscopic data of the synthetic **5** were well matched with those of natural **5**. The optical rotation of the synthetic **5** [$[\alpha]_D^{27}$ −58 (*c* 0.18, $CHCl_3$) for synthetic, $[\alpha]_D^{20}$ −57 (*c* 0.10, $CHCl_3$) for natural] established the absolute stereochemistry of natural **5** as depicted.



Scheme 3. Reagents and conditions: (i) $Hg(ClO_4)_2 \cdot 3H_2O$, MeOH:$CHCl_3$ (3:1) (86%); (j) 1.0 M KOHaq, *t*-BuOH, 50°C; (k) Na_2RuO_4, 1.0 M NaOHaq (95%); (l) DIBAL-H, CH_2Cl_2, −78°C (67%, 30% recovery of **19**); (m) 1.0 M HClaq, THF, 30 min (58%); (n) DMSO, Ac_2O (72%); (o) 6.0 M HClaq, THF, 50°C, 18 h (43%)

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References

1. Kuschel, A.; Anke, T.; Velten, R.; Klostermeyer, D.; Steglich, W.; König, B. *J. Antibiot.* **1994**, *47*, 733.
2. Velten, R.; Klostermeyer, D.; Steffan, B.; Steglich, W.; Kuschel, A.; Anke, T. *J. Antibiot.* **1994**, *47*, 1017.
3. Ayer, W. A.; Craw, P. A. *Can. J. Chem.* **1989**, *67*, 1371.
4. Velten, R.; Steglich, W.; Anke, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1229.
5. Murata, T.; Ishikawa, M.; Nishimaki, R.; Tadano, K. *Synlett* **1997**, 1291.
6. A recent report on natural product synthesis based on the IMDA approach, see: Ishihara, J.; Yamamoto, Y.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 4387.
7. For instance, we met difficulty in the oxidation of the hydroxylmethyl group, obtained by removal of the O-SEM group in **10**, for generation of an aldehyde group.
8. All new compounds were fully characterized by spectroscopic means [^1H (300 MHz in $CDCl_3$) and ^{13}C (75 MHz in $CDCl_3$) NMR, IR], and gave satisfactory HRMS except unstable intermediates. Yields refer to homogeneous samples purified by chromatography on silica gel.

9. Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743.
10. **22** as a colorless oil: $[\alpha]_D^{27}$ +121 (c 0.34, $CHCl_3$); ^1H NMR δ 1.02, 1.31 (2s, 3H×2), 1.59 (dd, *J*=3.7, 12.5, 1H), 1.86 (t, *J*=12.5 Hz, 1H), 2.12–2.17 (m, 1H), 2.68–2.76 (m, 1H), 3.35, 3.44, 3.47 (3s, 3H×3), 3.82–3.85 (m, 1H), 3.86 (dd, *J*=5.4, 10.7, 1H), 4.20 (ddd, *J*=2.2, 3.7, 12.5 Hz, 1H), 4.64 (s, 2H), 4.77, 4.98 (ABq, *J*=6.3 Hz, 1H×2), 5.10 (d, J=2.2 Hz, 1H), 5.82 (dt, *J*=2.4, 9.8 Hz, 1H), 5.99 (d, *J*=5.4 Hz, 1H), 6.01 (dt, *J*=3.7, 9.8 Hz, 1H); ^{13}C NMR δ 23.1, 33.0, 33.5, 39.3, 42.1, 42.6, 47.4, 55.6, 56.0, 56.6, 57.4, 72.7, 75.2, 95.3, 98.7, 104.2, 111.6, 127.1, 131.4, 174.0. HRMS calcd for $C_{20}H_{30}O_8$ (M^+), *m/z* 398.1940, found 398.1932. **5** as a colorless oil: ^1H NMR (CD_3OD) δ 1.02, 1.27 (2s, 3H×2), 1.40 (dd, *J*=3.9, 12.7 Hz, 1H), 1.64 (dd, *J*=3.4, 12.7 Hz, 1H), 1.87 (dd, *J*=12.5, 12.7 Hz, 1H), 2.06–2.20 (m, 1H), 2.50 (ddd, *J*=3.4, 6.6, 19.3 Hz, 1H), 3.73 (br s, 1H), 4.09 (ddd, *J*=2.4, 3.9, 12.5 Hz, 1H), 4.34 (br s, 1H), 5.39 (br s, 1H), 7.22 (br d, *J*=6.6 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (CD_3OD) δ 24.1, 26.0, 34.0, 34.5, 41.1, 42.3, 48.1, 55.7, 67.0, 72.5, 101.8, 140.5, 156.5, 179.1, 195.3. HRMS calcd for $C_{15}H_{20}O_6$ (M^+), *m/z* 296.1260, found 296.1263.