Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1801-1804, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00173-1

Total Synthesis of (±)-Stemodinone

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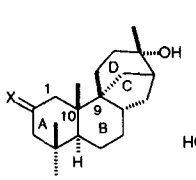
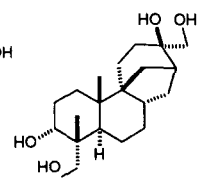
Abstract: Starting from methyl-olefin (**5**), the total synthesis of (±)-stemodinone (**2**) was achieved through an efficient ring-exchange reaction to control the stereochemistry of C10 followed by A-ring construction and the introduction of three methyl groups.

Stemodia maritima L. (Scrophulariaceae) has been used as a folk medicine in the Caribbean Islands for the treatment of venereal disease. Stemodin (**1**) and stemodinone (**2**), typical stemodane-type diterpenes that have been isolated as metabolites from this plant,[1] possess a unique tetracyclic skeleton: a *trans* decalin system (A/B-ring) fused to a bicyclo[3.2.1]octane system (C/D-ring), which is the same planar structure as aphidicolin (**3**), a potential antitumor and antiviral agent. Because of the remarkable biological activities of **3**,[2] considerable effort has been directed toward synthesizing these diterpenes.[3] One of the most important challenges in the synthesis of these diterpenes is the construction of two adjacent quaternary carbon centers (C9 and C10). We previously developed two methods for controlling the stereochemistry at C9[4,5] and successfully synthesized **3** starting from tricyclic ketone **4**.[6] In this paper, we describe a novel total synthesis of (±)-**2** starting from tricyclic methyl-olefin **5** which was selectively obtained from the same starting material as **4**[5b] *via* a tricyclic dienol ether **6**.



1 : X = α-OH, β-H
2 : X = O



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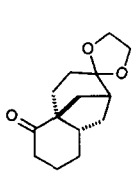

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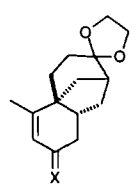
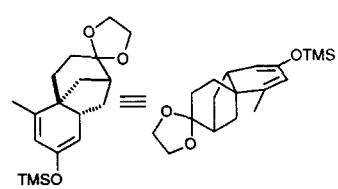


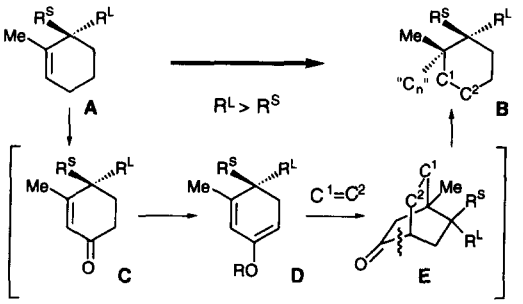
5 : X = H_2
7 : X = O



6

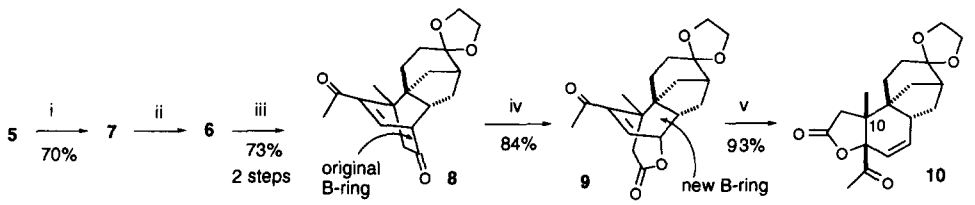
Since the stereochemistry of C9 has been established, our next goal was the proper construction of C10. Focusing on the structure of the dienol ether **6**, we required a method to introduce the carbon moiety ("C_n") to **6** from the more hindered α-side (*e.g.*, **A**→**B**) (Scheme 1). Therefore, we devised the following new ring-exchange strategy.[7] Methyl-olefin **A** was converted to dienol-ether **D** *via* enone **C**, and subsequent Diels-Alder reaction of **D** with a suitable dienophile (C^1=C^2) from the less hindered β side led to the bicyclo[2.2.2]octanone derivative **E**. Selective cleavage of the original ring gave **B** with a complete control of stereochemistry. This type of ring-exchange reaction should be useful for controlling the stereochemistry at

C10 in stemodanes and may also be applicable to the synthesis of other natural products.



Scheme 1

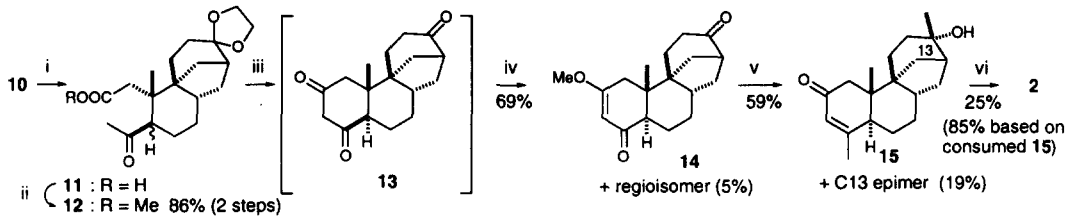
Following the strategy described in Scheme 1, we worked toward the stereospecific construction of C10. Methyl-olefin **5** gave enone **7** by allylic oxidation.[8] Enone **7** was converted to the dienol ether **6**, which was subjected to Diels-Alder reaction with 3-butyn-2-one followed by desilylation of the resulting silyl enol ether to give the bicyclic enedione **8**.# The structure of **8** was confirmed by X-ray crystallographic analysis, which revealed that the new ring was built from the less hindered β-side, as expected.[9] Regio- and chemoselective Baeyer-Villiger oxidation of **8** afforded the enone lactone **9** in good yield. The bicyclic 7-membered lactone **9** was easily isomerized in excellent yield to the fused 5-membered lactone **10**# by a Pd(0)-catalyzed lactone migration reaction[7] (Scheme 2).



Scheme 2 *Reagents and conditions* i, CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, -20 °C; ii, LDA, TMSCl, −78→0°C; iii, 3-butyn-2-one, neat, r.t., then *n*-Bu_4NF; iv, *m*-CPBA, NaH_2PO_4, toluene, r.t.; v, $Pd(Ph_3P)_4$, *n*-Bu_3P, MeCN, r.t.

Since C10 was constructed properly, we turned our efforts to constructing the A-ring and subsequent completion of the total synthesis. Hydrogenolysis of **10** gave the keto-acid **11** as a diastereomeric mixture with respect to the acetyl group (*ca. trans/cis* = 5.3/1).[10] Esterification with $TMSCHN_2$ in MeOH[11] gave keto-ester **12**. Base-promoted cyclization (NaH in the presence of a catalytic amount of MeOH in benzene) between the ester group derived from the original B-ring and the acetyl group introduced by Diels-Alder reaction followed by acidic workup gave only A/B-*trans* triketone **13**,[12] which was converted into the methoxy-enone **14** (69%) with a regioisomer (5%) under acidic equilibrium conditions.[13] One-pot introduction of two methyl groups to **14** was achieved by treatment with MeLi (10 equiv.) in the presence of lithium perchlorate (5 equiv.),[14] and this was followed by aqueous acidic workup to give a mixture of enone **15**# (59 %) and its C13-epimer (19 %),[15] which were then separated. Finally, conjugate addition of a methyl group (Me_2CuLi-TMSCl-HMPA in Et_2O)[16,17] to enone **15** resulted in the total synthesis of (±)-stemodinone (**2**) [mp 203-205 °C

(lit.[3a] 199-201 ℃)] in 25 % yield (85 % based on the consumed starting enone **15**).[18] The ^{1}H- and ^{13}C-NMR spectra of the synthetic **2** were identical to those of an authentic sample (Scheme 3). Since **2** has previously been converted to **1**,[3a] our synthesis of **2** also represents a total synthesis of (±)-stemodin **1**.



Scheme 3 *Reagents and conditions* i, H_2, Pd-C, MeOH-THF (1:1); ii, $TMSCHN_2$, MeOH; iii, NaH, MeOH, benzene; iv, 5 % HCl-MeOH solution; v, MeLi, $LiClO_4$, Et_2O then 10 % HCl; vi, Me_2CuLi, TMSCl, HMPA, Et_2O, then satd. $NaHCO_3$.

Acknowledgment The authors are indebted to Professor J. D. White, Oregon State University, for his generous supply of authentic natural stemodinone and its physical data. This research was supported in part by a Grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (No. 07672264).

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9 We have deposited *crystal data* for **8** with the Cambridge Crystallographic Data Centre (CCDC).

10 Attempted hydrogenolysis of the tetracyclic lactone **9** to **11** using a Pd-C catalyst resulted in the formation of a saturated 7-membered lactone as the major product. Under the conditions of Pd(0) with ammonium formate (*Cf.* Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1-24.), only **10** was rapidly obtained without the formation of any reduction products. The *trans*- and *cis* keto-ester mixture of **12** was separable. Their stereochemistries were confirmed by NOE experiments between the methyl group and the adjacent methine proton, and this showed that the main product was the *trans* isomer.

11 Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475-1478.

12 The mixture of *trans* and *cis* keto-ester **12** gave only *trans* triketone **13** after base-promoted cyclization followed by workup with a strong acid. Therefore, we performed this synthesis without separating the isomers of **12**.

13 Brossi, A.; Baumann, M.; Gerecke, M.; Kyburz, E. *Helv. Chim. Acta* **1960**, *43*, 2071-2082; Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 4597-4600; White, J. D.; Noren, Jr. E. G.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150-1152.

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15 The stereoselectivity of D-ring methylation is usually not high. The best result known to date is 6:1 with methyltitanium triisopropoxide reported by Piers *et al.*[3e] However, these conditions were not applicable to compound **14** due to the formation of a complex mixture. The stereochemistry of C13 in **15** and its epimer was determined by comparing the chemical shifts (δ 1.14 for **15**, 1.24 for the epimer) of the methyl group at C13 with that of 2-desoxystemodinone (δ 1.12) and its epimer (δ 1.23).[3f]

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17 A recent review of organocopper reagents, see: "Organocopper Reagents," ed. by Taylor, R. J. K., Oxford University Press, 1994.

18 Strangely, conjugate addition was not complete under several reaction conditions (for example, Me_2CuLi, Me_2CuLi-H_2O, Me_2CuLi-TMSCl, Me_2CuLi-TMSCl-HMPA) and most of the starting enone was recovered. The optimal reaction conditions remain to be determined.

Selected physical data for **8**: mp 144-145 ℃; ^{1}H-NMR (200 MHz) 1.11 (1H, m), 1.38 (3H, s), 1.40-1.45 (2H, m), 1.56-1.62 (2H, m), 1.72-1.81 (2H, m), 1.90 (1H, m), 2.01 (1H, m), 2.03 (1H, d, J = 18.0 Hz), 2.21 (1H, m), 2.28 (1H, d, J = 18.0 Hz), 2.31 (3H, s), 3.07 (1H, dd, J = 6.4, 2.4 Hz), 3.79-3.99 (4H, m), 7.08 (1H, d, J = 6.4 Hz); ^{13}C-NMR (67.8 MHz) 17.94, 27.89, 30.28, 30.60, 32.63, 33.10, 44.12, 47.12, 48.36, 49.00, 49.65, 54.99, 64.37, 110.60, 140.68, 151.43, 197.91, 211.61. **10**: mp 231-233 ℃; ^{1}H-NMR (500 MHz) 1.07 (3H, s), 1.47-1.69 (5H, m), 1.79 (1H, ddd, J = 13.6,13.6, 6.0 Hz), 1.87 (1H, m), 2.10 (1H, m), 2.18 (1H, m), 2.25 (3H, s), 2.38 (1H, d, J = 17.5 Hz), 2.47 (1H, m), 2.69 (1H, d, J = 17.5 Hz), 3.80-3.95 (4H, m), 5.70 (1H, dd, J = 10.3, 2.1 Hz), 6.05 (1H, dd, J = 10.3, 2.1 Hz); ^{13}C-NMR (67.8 MHz) 19.64, 28.84, 29.00, 29.04, 34.36, 34.97, 38.06, 38.64, 41.98, 44.98, 45.66, 64.01, 64.49, 88.41, 110.01, 116.77, 140.50, 175.58, 207.33. **15**: mp 175-177 ℃; ^{1}H-NMR (500 MHz) 0.94 (3H, s), 1.14 (3H, s), 1.24-1.40 (6H, m), 1.56 (1H, ddd, J = 12.6, 12.6, 6.0 Hz), 1.66 (1H, ddd, J = 12.6, 12.6, 6.0 Hz), 1.71-1.85 (5H, m), 1.90 (3H, s), 1.96-2.05 (2H, m), 2.33 (1H, d, J = 15.5 Hz), 2.53 (1H, d, J = 15.5 Hz), 2.60 (1H, m), 5.89 (1H, m); ^{13}C-NMR (126 MHz) 17.68, 22.84, 22.89, 27.88, 28.29, 30.57, 32.59, 35.18, 36.32, 38.00, 41.76, 44.17, 45.92, 48.26, 48.72, 72.21, 126.41, 163.48, 199.67.

(*Received in Japan* 16 *December* 1996; *accepted* 16 *January* 1997)