Total Synthesis of (±)-Stemodinone via an Efficient Ring-Exchange Strategy

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A total synthesis of (±)-stemodinone, a tetracyclic stemodane diterpene, from the known tricyclic methyl olefin **11** is described. The key steps involve an efficient ring-exchange reaction and palladium(0)-catalyzed lactone migration. The ring-exchange strategy for controlling the stereochemistry was based on an initial Diels−Alder reaction to form a new ring followed by cleavage of the original ring. Cleavage of the original ring of the Diels−Alder adduct **9** was achieved by an initial regio- and chemoselective Baeyer−Villiger oxidation followed by the Pd(0)-catalyzed lactone-migration reaction reported by us.

Introduction

The leaves of the rare littoral plant *Stemodia maritima* L. (family Scrophulariaceae) have long been used as a folk medicine in the Caribbean Islands for the treatment of venereal disease.[1] Attracted by the reported medicinal properties, Manchand and co-workers carried out phytochemical investigations on this plant in 1973 to isolate and characterize two structurally unique tetracyclic diterpenes, stemodin (**1**) and stemodinone (**2**).[2] The structures of the two diterpenes were confirmed by X-ray crystallography and also by the chemical correlation between them; Jones oxidation of stemodin (**1**) gave stemodinone (**2**). Further investigation on this plant by different groups resulted in isolation and characterization of 2-desoxystemodinone (**3**),[3] maritimol (**4**),[4] and stemarin (**5**);[5] the latter exhibited another new diterpene skeleton. Earlier, Hesp and co-workers isolated a tetracyclic tetraol aphidicolin (**6**) from *Cephalalosporium aphidicola*[6] and later found it to occur in *Nigrosporum sphaerica*. Aphidicolin is widely known as a potent antitumor (inhibits DNA replication and growth of several human and marine neoplastic cells)[7] and antiviral agent (promising activity against Herpes simplex).[8] Stemodanes **1**−**4** and aphidicolin **6** are structurally related to each other in having a similar tetracyclic ring system, differing mainly in the stereorelationship of the C and D rings. The fusion of the five-membered C ring to B in stemodanes is cis in contrast to the trans fusion in aphidicolin. Both diterpene families have the bicyclo[3.2.1]octane moiety (C/D ring system) fused with a *trans*-decalin moiety (A/B ring system) (Figure 1).

Stemodane diterpenes, by virtue of their unique tetracyclic carbon skeleton, the alleged medicinal properties of *Stemodia maritima*, and their close structural resemblance with aphidicolin, prompted a considerable number of synthetic investigations on this diterpene family. The presence of more than six stereocenters and four quaternary carbons, especially the two adjacent quaternary carbons at C-9 and C-10, makes them a worthy synthetic challenge. Although several synthetic pathways to members of the stemodane family were known,[9] two precedent syntheses of stemodinone were reported before our synthesis.[9a,b] While Corey and co-workers reported a

† Osaka University.
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(9) For the previously reported synthetic methods of (±)-stemodinone, see: (a) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7612. (b) Lupi, A.; Patamia, M.; Grgurina, I.; Bettolo, R. M.; Leo, O. D.; Gioia, P.; Antonaroli, S. *Helv. Chim. Acta* **1984**, *67*, 2261. For the synthesis of other stemodanes, see: (c) van Tamelen, E. E.; Carlson, J. G.; Russel, R. K.; Zawacky, S. R. *J. Am. Chem. Soc.* **1981**, *103*, 4615. (d) Kelly, R. B.; Harley, M. L.; Alward, S. J.; Rej, R. N.; Gowda, G.; Mukhopadhyay, A.; Manchand, P. S. *Can. J. Chem.* **1983**, *61*, 269 and their related works cited therein. (e) Piers, E.; Abeysekera, B. F.; Herbert, D. J.; Suckling, I. D. *Can. J. Chem.* **1985**, *63*, 3418. (f) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424. (g) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 9912. (h) Germanas, J.; Aubert, C.; Volhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006. (i) Rizzo, C. J.; Smith, A. B., III. *J. Chem. Soc., Perkin Trans. 1* **1991**, 969. (j) Toyota, M.; Seishi, T.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 3673 and their related works cited therein. (k) Hegarty, P.; Mann, J. *Tetrahedron* **1995**, *51*, 9079. (l) Pearson, A. J.; Fang, X. *J. Org. Chem.* **1997**, *62*, 5284. (m) Toro, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526. (n) For a review on the synthesis of aphidicolane and stemodane diterpenes, see: Toyota, M.; Ihara, M. *Tetrahedron* **1999**, *55*, 5641.

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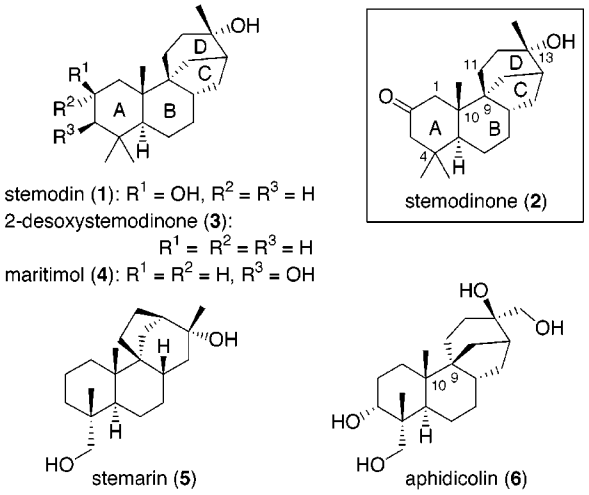
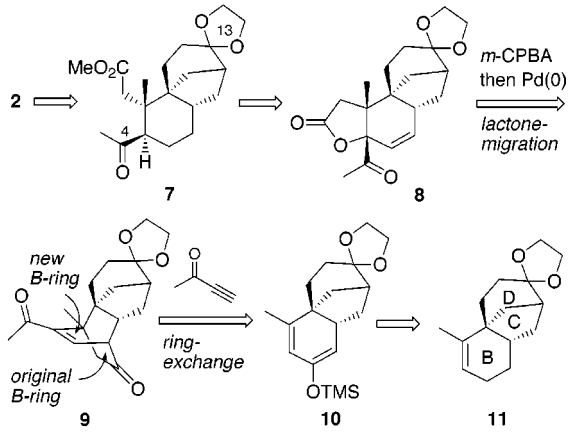


Figure 1.

Scheme 1

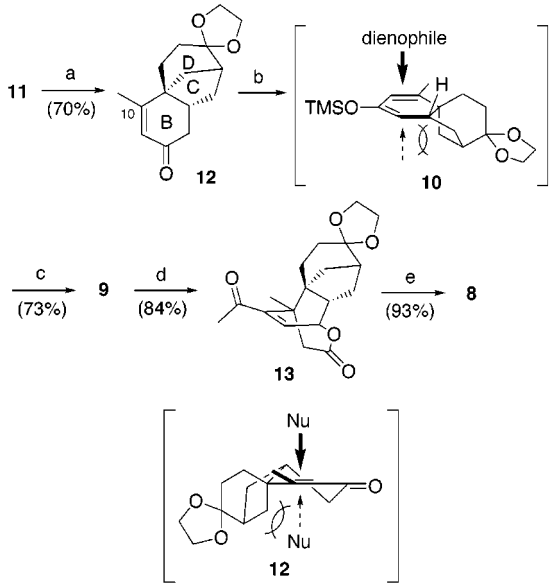


synthesis of (±)-stemodinone from an analogue of the A/B ring system,[9a] Bettolo and his associates synthesized the same from a precursor of the A/B/C ring system.[9b] Herein, we describe a synthesis of (±)-stemodinone from a B/C/D ring precursor utilizing some interesting strategies that completely differ from those reported.[10]

Results and Discussion

Synthetic Plan. Our synthetic studies on stemodinone are based on an initial formation of the B/C/D ring system followed by construction of the A ring with the requisite functionalities and stereochemical configuration. Our basic strategy is outlined in Scheme 1. The central strategic point of our plan is the efficient ring-exchange reaction to control the stereochemistry of C-10[11] followed by A ring construction. We envisaged that synthesis of stemodinone **2** would be possible by cyclization of the keto ester **7** to form the A ring, followed by introduction of three methyl groups at C-4 and C-13 (stereoselectively). The keto ester **7** was assumed to derive from the five-membered lactone **8** by hydrogenolysis followed by esterification. Access to **8** was expected from **9** via a regioselective Baeyer−Villiger oxidation of the enedione **9** and subsequent utilization of our Pd(0)-catalyzed lactone migration reaction[12] of the resultant bicyclic seven-membered lactone. The enedione **9** might be synthesized by the Diels−Alder reaction of the silyl dienol ether **10** with 3-butyn-2-one and subsequent desilylation of the resulting silyl enol ether. Dienol ether **10** could be prepared in a straightforward manner from the B/C/D analogue **11**, the stereoselective synthesis of which was previously reported from our laboratory.[13]

Scheme 2[a]

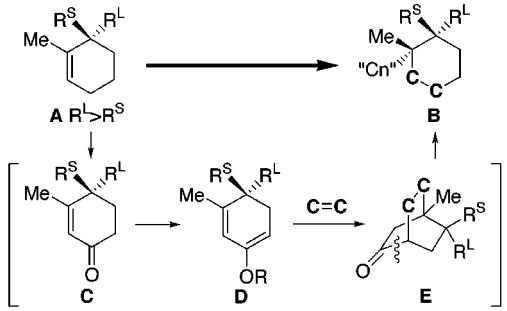


[a] Reagents and conditions: (a) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −20 °C; (b) LDA, TMSCl, −78 to 0 °C; (c) 3-butyn-2-one, neat, rt; *n*-Bu_4NF, THF; (d) *m*-CPBA, NaH_2PO_4, toluene, rt; (e) $Pd(PPh_3)_4$, PBu_3, MeCN, rt.

Stereocontrolled Construction of a Quaternary Carbon at C-10. Starting from the B/C/D analogue **11**,[13] we initially focused on the stereoselective formation of a quaternary carbon at C-10. As depicted in Scheme 2, allylic oxidation[14] of the methyl olefin **11** gave the enone

(10) In a preliminary communication, we outlined our work briefly: Tanaka, T.; Murakami, K.; Kanda, A.; Patra, D.; Yamamoto, S.; Satoh, N.; Kim, S.-W.; Ishida, T.; In, Y.; Iwata, C. *Tetrahedron Lett.* **1997**, *38*, 1801.

(11) The ring-exchange strategy[12] involves the carbon−carbon bond formation to the methyl olefin **A** from the more hindered α-side ($R^L > R^S$) to generate a quaternary carbon in a fully stereoselective fashion (e.g., **A** → **B**). The sequential steps are the conversion of the methyl olefin **A** into dienol ether **D** via **C**, and subsequent Diels−Alder reaction of **D** with a suitable dienophile (C=C) from the less hindered *β*-side to give a bicyclo[2.2.2]octane derivative **E**. Selective cleavage of the original ring would give **B** with complete control of stereochemistry. We speculated that this type of ring-exchange reaction would be useful for controlling the stereochemistry at C-10 in stemodanes and may also be applicable to the synthesis of other natural products.



(12) Tanaka, T.; Patra, D.; Murakami, K.; Kanda, A.; Hamano, K.; Yamamoto, S.; Satoh, N.; Iwata, C. *Tetrahedron Lett.* **1996**, *37*, 7809.

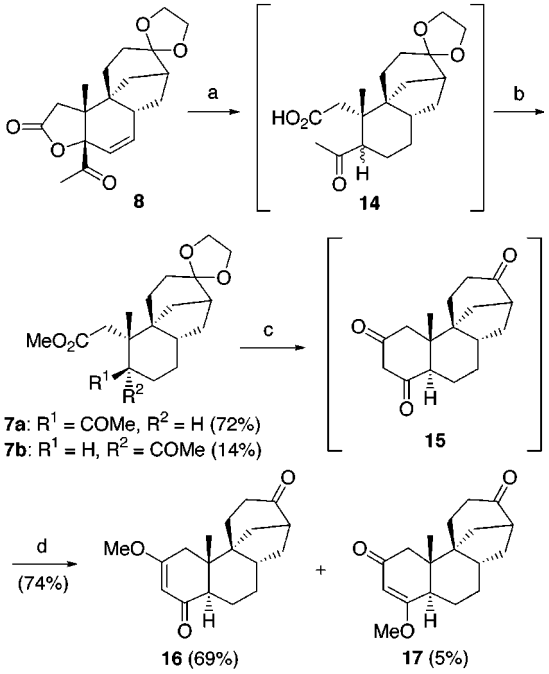
(13) (a) Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Iwata, C. *Tetrahedron Lett.* **1994**, *35*, 4125. (b) Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 1017.

12 in good yield. Although formation of a quaternary carbon at C-10 via 1,4-addition might be possible, we speculated that this reaction would lead to an undesired product; that is, the C/D ring bicyclooctane moiety would favor β-face addition of a nucleophile (structure **12** within the bracket), to give an addition product with an undesired stereochemical configuration.[15] Therefore, we explored a different route via the dienol ether **10**, which was derived from **12** by the treatment of LDA in the presence of trimethylsilyl chloride (TMSCl). For the generation of a quaternary carbon with the requisite stereochemistry, we required a method to introduce a suitable carbon moiety at C-10 from the more hindered α-side. We anticipated that this could be possible by a ring-exchange strategy.[11] Thus, the crude ether **10**, without further purification, was converted to the bicyclic enedione **9** via Diels−Alder reaction with 3-butyn-2-one, followed by desilylation of the resulting silyl enol ether.[17]

Bearing in mind our main goal, i.e., stereoselective generation of a quaternary carbon at C-10, we next applied our reported strategy[12] to the conversion of **9** into **8**. Regio- and chemoselective Baeyer−Villiger oxidation of **9** by *m*-CPBA in the presence of a phosphate buffer (NaH_2PO_4) afforded the enone lactone **13** in 84% yield. The bicyclic seven-membered lactone **13** was then easily isomerized to the cis-fused five-membered lactone **8** having the desired stereochemical feature at C-10, by the Pd(0)-catalyzed lactone migration reaction.[12]

Construction of the A Ring and Completion of the Total Synthesis. Elaboration of the A ring from the five-membered lactone **8** and subsequent functionalization remained to be accomplished to complete the synthesis of stemodinone. To achieve this, **8** was exposed to hydrogen atmosphere in the presence of Pd/C (Scheme 3). Simultaneous hydrogenolysis of the lactone and hydrogenation of the olefin proceeded to give a diastereoisomeric mixture of the keto acid **14**,[18] which was not separated. Esterification of the crude mixture of **14** with $TMSCHN_2$ in MeOH[20] provided a diastereoisomeric mixture of **7a** and **7b** (**7a**/**7b** = 5.3:1).[21,22] Although separation of the two isomers was possible, we were pleased to find that only the trans-fused triketone **15** was derived from the mixture of the keto esters **7a** and **7b** by the base-promoted cyclization (NaH in benzene−MeOH) followed by acidic workup.[23] The crude triketone **15** was then converted into the methoxy enone **16** (69% yield) with its minor regioisomer **17** (5%) under acidic equilibrium conditions.[24,25]

Scheme 3[a]



[a] Reagents and conditions: (a) H_2, 10% Pd/C, MeOH−THF (1:1), rt; (b) $TMSCHN_2$, MeOH, rt; (c) NaH, benzene−MeOH; (d) 5% HCl, MeOH.

Completion of the synthesis of stemodinone further required introduction of three methyl groups at C-4 and

(14) (a) Salmond, W. G.; Barta, M. A.; Havenes, J. L. *J. Org. Chem.* **1978**, *43*, 2057. (b) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146.

(15) Such type of β-face adduct was obtained exclusively using a similar enone in our total synthesis of aphidicolin.[16]

(16) (a) Tanaka, T.; Murakami, K.; Okuda, O.; Inoue, T.; Kuroda, T.; Kamei, K.; Murata, T.; Yoshino, H.; Imanishi, T.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 193. (b) Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 1407.

(17) We have deposited the *crystal data* for **9** with the Cambridge Crystallographic Data Center (CCDC). The data can be obtained on request from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.

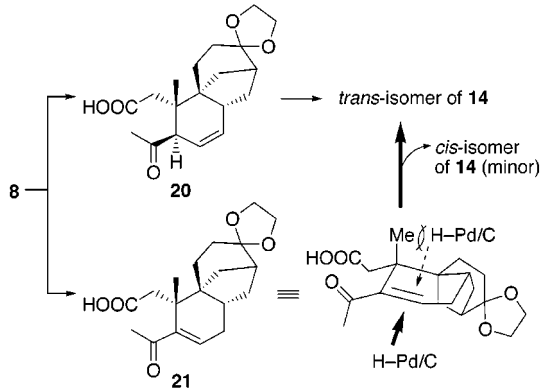
(18) Attempted hydrogenolysis of the tetracyclic lactone **13** to **14** using a Pd/C catalyst resulted in the formation of a saturated seven-membered lactone as the major product. Under the conditions of Pd-(0) with ammonium formate,[19] only **8** was rapidly obtained without formation of any reduction product.

(19) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1.

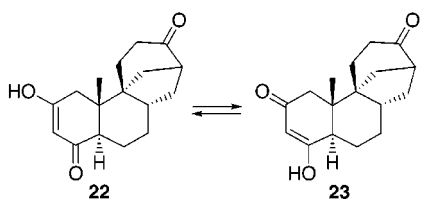
(20) Hashimoto, N.; Aoyoma, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

(21) The two isomers were identified by NOE experiments between the C-10 methyl group and the adjacent C-5 methine proton. The C-10 methyl of the major trans isomer resonated at δ 1.24 and that of the cis isomer resonated at δ 1.08.

(22) Our assumption was that the conversion of **8** into **14** passed through **20** and/or **21**. While hydrogenation of **20** would lead to the trans isomer exclusively, that of **21** would also favor formation of the trans isomer because of the steric repulsion of the active hydrogen donor (H−Pd/C complex) with the Me group.



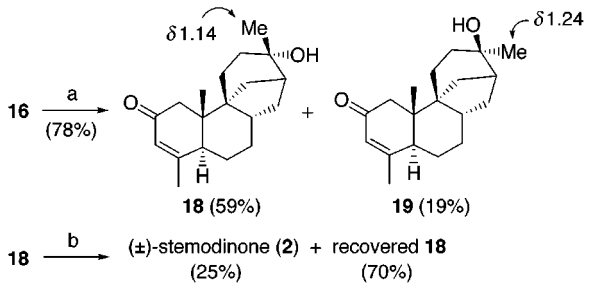
(23) The triketone **15** exists as 1:1 mixture of the enols **22** and **23** in $CDCl_3$.



(24) (a) Brossi, A.; Baumann, M.; Gerecke, M.; Kyburz, E. *Helv. Chim. Acta* **1960**, *43*, 2071. (b) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 4597. (c) White, J. D.; Noren, E. G., Jr.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150.

(25) In the methanolic acidic solution, the equilibrium between the enolates **16** and **17** shifted towards the former.

Scheme 4[a]



[a] Reagents: (a) MeLi, $LiClO_4$, Et_2O, then 10% HCl; (b) Me_2CuLi, TMSCl, HMPA, Et_2O, then saturated $NaHCO_3$.

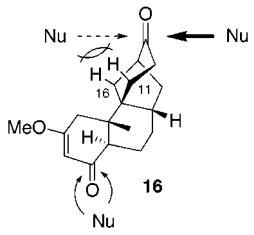


Figure 2. Stereoselective methylation of **16**.

C-13, the latter of which should be introduced in a stereoselective fashion. Since the tertiary alcohol at C-13 of stemodinone is axially oriented, a methylating agent that preferably reacts from the equatorial side would be suitable for the selective generation of the axial alcohol at C-13. In addition, simultaneous methylation at C-4 would be desirable. Several reagents were reported to attack from the equatorial side.[9a,e−g,26] Among the reagents used for the stemodane nucleus so far, $MeTi(OPr^i)_3$ was reported to give the best result (selectivity = 6:1).[9e] However, when **16** was allowed to react with $MeTi(OPr^i)_3$, formation of a complex mixture resulted. In contrast, when **16** was treated with MeLi (10 equiv) in the presence of lithium perchlorate (5 equiv),[26a] one-pot introduction of two methyl groups at C-4 and C-13 prevailed. After aqueous acidic workup, the desired enone **18** (59%) and its C-13 epimer **19** (19%) (78% combined yield) were isolated (Scheme 4). The stereochemistry of C-13 of **18** and **19** was determined by comparing the chemical shift values of the methyl group at C-13 (δ 1.14 for **18**, δ 1.24 for **19**) with those of 2-desoxystemodinone (δ 1.12 for equatorial methyl of 2-desoxystemodinone and δ 1.23 for the axial methyl of its C-13 epimer). As shown in Figure 2, the preferred formation of the equatorial adduct **18** would be attributed to the steric repulsion of the reagent with the axial hydrogens at both C-11 and C-16.

Finally, introduction of the remaining methyl group at C-4 was targeted. Organocopper-catalyzed 1,4-addition was investigated. Several reaction conditions (Me_2CuLi, $Me_2CuLi-H_2O$, $Me_2CuLi-TMSCl$, $Me_2CuLi-TMSCl-HMPA$, $MeCu-PBu_3$, and $Me_2CuLi\cdot LiCN$, etc.)[27] were employed to introduce the methyl group at C-4. However, the reactions proceeded sluggishly to give very low yields of stemodinone (**2**) in most of the cases, and a large amount of the starting enone was recovered. The best result obtained was 25% yield of stemodinone (**2**) together with 70% of the recovered starting material by using $Me_2CuLi-TMSCl-HMPA$.[28] Although the yield of this reaction was very poor, the recovered starting material was recyclable. Soon after our preliminary report on this work was published,[10] Pearson and Fang reported the synthesis of **18** in a different manner. For improvement of the yield of **2**, they examined a variety of other conjugate addition methods; however, their attempts were also unsuccessful.[9l]

Our synthetic stemodinone (**2**) showed TLC behavior and ^1H and ^{13}C NMR spectra which were identical to those of an authentic sample of the natural stemodinone. Our measured melting point of the synthetic (±)-stemodinone (203−205 °C) differed slightly from the literature value (199−201 °C).[9a] It should be pointed out that **2** has been previously converted to **1**[9a] and **3**.[2] Therefore, our synthesis of **2** also represents formal total syntheses of (±)-stemodin (**1**) and (±)-2-desoxystemodinone (**3**).

Conclusion

We have developed a unique synthetic route toward the stemodane diterpenes. Our new synthetic route employed an efficient ring-exchange reaction to control the stereochemistry at C-10, a ring-opening and subsequent ring closure for the construction of the A ring, and a one-pot stereoselective method for introduction of two methyl groups. Although the synthesis of stemodinone was accomplished in eleven steps from **11**, some of the intermediates did not require purification, which simplified the operation. The only problematic step is the final conjugate addition of a methyl group; however, it seems that this is insurmountable at the present time.

Experimental Section

General Methods. Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, dt = double triplet, td = triple doublet, m = multiplet). For column chromatography, silica gel 60 (0.063−0.200 mm, Merck) was employed.

(±)-(1*R*,6*R*,8*S*)-2-Methyltricyclo[6.3.1.0^{1,6}]dodec-2-ene-4,9-dione 4,4-Ethylene Acetal (12). To a suspension of CrO_3 (3.6 g, 36 mmol) in CH_2Cl_2 (46 mL) was added 3,5-dimethylpyrazole (3.44 g, 36 mmol) in one portion at −20 °C with vigorous stirring, and the mixture was stirred for 15 min. A solution of **11** (590 mg, 2.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the above stirred reagent, and the mixture was stirred for 2 h. After CH_2Cl_2 (120 mL) and SiO_2 (25 g) were added to the mixture, the whole was filtered through a pad of Florisil with Et_2O, and the eluate was concentrated. The concentrate was dissolved in EtOAc, and the solution was washed with 10% HCl, water, saturated $NaHCO_3$, water, and brine, dried, and concentrated. The concentrate was purified by column chromatography (2:1 *n*-hexane/EtOAc) to give **12**

(26) (a) Ashby, E. C.; Nodling, S. A. *J. Org. Chem.* **1979**, *44*, 4371. (b) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. (c) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. (d) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441.

(27) (a) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Synder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023. (b) For a recent review on organocopper reagent, see: *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994.

(28) Introduction of the remaining methyl group at C-4 was extremely difficult, presumably due to the steric hindrance imposed by the methyl groups at both C-4 and C-10. We also experienced such difficulties using similar enones in our synthetic studies on scopadulin; see: Rahman, S. M. A.; Ohno, H.; Yoshino, H.; Satoh, N.; Tsukaguchi, M.; Murakami, K.; Iwata, C.; Maezaki, N.; Tanaka, T. *Tetrahedron* **2001**, *57*, 127.

(440 mg, 70% yield): colorless crystals; mp 97−99 °C (*n*-hexane); IR (KBr) cm^{-1} 1672, 1620; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.39 (ddd, J = 14.2, 6.5, 4.3 Hz, 1H), 1.67 (m, 1H), 1.76 (m, 1H), 1.80 (dd, J = 14.2, 6.5 Hz, 1H), 1.95 (s, 3H, 2-Me), 2.04 (ddd, J = 14.2, 14.2, 6.5 Hz, 1H), 2.07 (d, J = 11.8 Hz, 1H), 2.11−2.36 (m, 4H), 2.48 (dd, J = 14.2, 5.4 Hz, 1H), 3.84−4.02 (m, 4H, OCH_2CH_2O), 5.80 (s, 1H, 3-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.2, 29.0, 34.5, 35.4, 35.6, 39.1, 44.1, 44.2, 46.6, 64.1, 64.6, 110.1, 126.1, 164.3, 199.0; MS (EI) *m*/*z* 248 (M^+). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.28; H, 8.20.

(±)-(1*R*,2*R*,6*S*,8*S*,9*S*)-1-Methyl-11-(1-oxoethyl)tetracyclo-[7.2.2.1^{2,6}.0^{2,8}]tetradec-10-ene-5,13-dione 5,5-Ethylene Acetal (9). A solution of **12** (640 mg, 2.6 mmol) in THF (10 mL) was added dropwise to LDA [0.48 M in THF−*n*-hexane (2:1); 16 mL, 7.7 mmol] at −78 °C, and the mixture was stirred for 15 min. After TMSCl (0.5 mL, 3.9 mmol) was added, the mixture was stirred with warming to 0 °C. Et_3N (1.0 mL, 7.2 mmol) was added to the mixture, and the mixture was concentrated. The residue was suspended in Et_2O and filtered, and the filtrate was concentrated to give crude silyl dienol ether **10**. 3-Butyn-2-one (1.0 mL, 13 mmol) was added to the crude **10**, and the mixture was stirred for 30 h. The mixture was concentrated to give a residual oil, which was dissolved in Et_2O (10 mL). *n*-Bu_4NF (1.0 M in THF; 3.0 mL, 3.0 mmol) was added to the mixture with stirring, and the mixture was stirred for 5 min. Water was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The concentrate was purified by column chromatography (4:1 *n*-hexane/EtOAc) to give **9** (595 mg, 73% yield): colorless crystals; mp 144−145 °C (*i*-Pr_2O); IR (KBr) cm^{-1} 1726, 1673, 1593; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (m, 1H), 1.38 (s, 3H, 1-Me), 1.40−1.45 (m, 2H), 1.56−1.62 (m, 2H), 1.72−1.81 (m, 2H), 1.90 (m, 1H), 2.01 (m, 1H), 2.03 (d, J = 18.0 Hz, 1H, 12-C*H*H), 2.21 (m, 1H), 2.28 (d, J = 18.0 Hz, 1H, 12-CH*H*), 2.31 (s, 3H, $COCH_3$), 3.07 (dd, J = 6.4, 2.4 Hz, 1H, 9-H), 3.79−3.99 (m, 4H, OCH_2CH_2O), 7.08 (d, J = 6.4 Hz, 1H, C=CH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 17.9, 27.9, 30.3, 30.6, 32.6, 33.1, 44.1, 47.1, 48.4, 49.0, 49.7, 55.0, 64.4 (2C), 110.6, 140.7, 151.4, 197.9, 211.6; MS (EI) *m*/*z* 316 (M^+). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.07; H, 7.65.

(±)-(1*R*,2*R*,6*S*,8*S*,9*S*)-1-Methyl-13-(1-oxoethyl)-10-oxatetracyclo[7.3.2.1^{2,6}.0^{2,8}]pentadec-14-ene-5,11-dione 5,5-Ethylene Acetal (13). To a stirred solution of **9** (372 mg, 1.2 mmol) in toluene (15 mL) were added 80% *m*-CPBA (800 mg, 3.7 mmol) and NaH_2PO_4 (800 mg, 6.7 mmol), and the mixture was stirred overnight at room temperature, followed by quenching with Me_2S (0.27 mL, 3.7 mmol). The whole was extracted with $CHCl_3$, and the extract was washed with water and brine, dried, and concentrated. The concentrate was purified by column chromatography (3:1 *n*-hexane/EtOAc) to give **13** (330 mg, 84% yield): colorless crystals; mp 150−152 °C (*i*-Pr_2O−$CHCl_3$); IR (KBr) cm^{-1} 1724, 1686; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.20 (s, 3H, 1-Me), 1.21 (m, 1H), 1.47 (ddd, J = 11.9, 5.1, 5.1 Hz, 1H), 1.65−1.72 (m, 3H), 1.75 (d, J = 11.9 Hz, 1H), 1.89−1.98 (m, 3H), 2.30 (m, 1H), 2.35 (s, 3H, $COCH_3$), 2.76 (s, 2H, 12-H), 3.84−4.00 (m, 4H, OCH_2CH_2O), 4.77 (dd, J = 6.8, 2.3 Hz, 1H, 9-H), 6.72 (d, J = 6.8 Hz, 1H, 14-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 20.9, 28.6, 29.6, 30.0, 33.9, 35.0, 39.7, 45.6, 46.9, 49.5, 64.4, 64.5, 72.9, 96.1, 110.2, 132.1, 154.4, 171.3, 200.4; MS (EI) *m*/*z* 332 (M^+). Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.50; H, 7.22.

(±)-(1*R*,2*R*,6*S*,9*R*,11*S*)-2-Methyl-6-(1-oxoethyl)-5-oxatetracyclo[9.3.1.0^{1,9}.0^{2,6}]pentadec-7-ene-4,12-dione 12,12-Ethylene Acetal (8). To a stirred solution of **13** (14 mg, 0.042 mmol) in MeCN (0.8 mL) were added $Pd(PPh_3)_4$ (5.0 mg, 4.2 mmol) and PBu_3 (4.2 mL, 0.017 mmol), and the mixture was stirred at room temperature for 1 h. Concentration under reduced pressure gave a residual oil, which was purified by column chromatography (1:1 *n*-hexane/EtOAc) to give **8** (13 mg, 93% yield): colorless crystals; mp 231−233 °C (*i*-Pr_2O−$CHCl_3$); IR (KBr) cm^{-1} 1788, 1759, 1718; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 3H, 2-Me), 1.47−1.69 (m, 5H), 1.79 (ddd, J = 13.6, 13.6, 6.8 Hz, 1H), 1.87 (m, 1H), 2.10 (m, 1H), 2.18 (m, 1H), 2.25 (s, 3H, $COCH_3$), 2.38 (d, J = 17.5 Hz, 1H, 3-C*H*H), 2.47 (m, 1H), 2.69 (d, J = 17.5 Hz, 1H, 3-CH*H*), 3.80−3.95 (m, 4H, OCH_2CH_2O), 5.70 (dd, J = 10.3, 2.1 Hz, 1H), 6.05 (dd, J = 10.3, 2.1 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.6, 28.8, 29.0, 29.0, 34.4, 35.0, 38.1, 38.6, 42.0, 45.0, 45.7, 64.0, 64.6, 88.4, 110.0, 116.8, 140.5, 175.6, 207.3; MS (CI) *m*/*z* 333 (MH^+). Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.30; H, 7.21.

Methyl (±)-(1*R*,2*S*,3*R*,6*S*,8*S*)-[9,9-Ethylenedioxy-2-methyl-3-(1-oxoethyl)tricyclo[6.3.1.0^{1,6}]dodec-2-yl]acetate (7a) and Its (1*R*,2*S*,3*S*,6*S*,8*S*)-Isomer (7b). To a solution of **8** (21 mg, 0.063 mmol) in a mixed solvent of THF (1 mL) and MeOH (1 mL) was added 10% Pd/C (10 mg), and the mixture was stirred for 6 h under hydrogen (1 atm) at room temperature. The mixture was filtered, and the filtrate was concentrated to give the crude acid **14**, which was dissolved in MeOH (1 mL). $TMSCHN_2$ (ca. 10 equiv) was added to the above stirred solution until **14** disappeared on TLC. The mixture was concentrated, and the residue was purified by column chromatography (1:1 *n*-hexane/EtOAc) to give **7a** (16 mg, 72% yield) and **7b** (3.0 mg, 14% yield).

Compound **7a**: colorless oil; IR (KBr) cm^{-1} 1730, 1709; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20−1.26 (m, 2H), 1.24 (s, 3H, 2-Me), 1.51−1.63 (m, 6H), 1.70−1.98 (m, 5H), 2.10 (m, 1H), 2.21 (s, 3H, $COCH_3$), 2.47 (d, J = 15.2 Hz, 1H), 2.61 (d, J = 15.2 Hz, 1H), 3.18 (m, 1H, 3-H), 3.60 (s, 3H, CO_2CH_3), 3.77−3.96 (m, 4H, OCH_2CH_2O); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.5, 24.7, 28.88, 28.93, 30.8, 32.4, 35.3, 36.7, 38.2, 39.6, 40.2, 42.9, 49.0, 51.2, 52.2, 63.9, 64.5, 111.2, 173.2, 212.3; MS (EI) *m*/*z* 350 (M^+). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.57; H, 8.46.

Compound **7b**: colorless oil; IR (KBr) cm^{-1} 1732, 1711; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.08 (s, 3H, 2-Me), 1.22−1.27 (m, 2H), 1.45−1.80 (m, 9H), 1.94−2.04 (m, 2H), 2.18 (s, 3H, $COCH_3$), 2.35 (m, 1H), 2.40 (d, J = 14.3 Hz, 1H), 3.05−3.09 (m, 2H), 3.59 (s, 3H, $COOCH_3$), 3.80−3.98 (m, 4H, OCH_2-CH_2O); MS (EI) *m*/*z* 350 (M^+).

(±)-(1*R*,2*S*,7*R*,10*S*,12*S*)-4-Methoxy-2-methyltetracyclo-[10.3.1.0^{1,10}.0^{2,7}]hexadec-4-ene-6,13-dione (16) and (±)-(1*R*,2*S*,7*R*,10*S*,12*S*)-6-Methoxy-2-methyltetracyclo-[10.3.1.0^{1,10}.0^{2,7}]hexadec-5-ene-4,13-dione (17). NaH (60% dispersion; 8.0 mg, 0.20 mmol; washed with *n*-hexane) and MeOH (1 mL) were added to a mixture of **7a** and **7b** (10 mg, 0.029 mmol) in benzene (5 mL), and the mixture was heated under reflux for 20 h. After cooling, the mixture was made acidic with 10% HCl, and the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated to give a crude triketone **15** (1:1 mixture of the enols **22** and **23** in $CDCl_3$).[23] The crude triketone was treated with 5% HCl in MeOH for 12 h at room temperature. The mixture was concentrated to give a residual oil, which was purified by preparative TLC (1:1 *n*-hexane/EtOAc) to give **16** (5.7 mg, 69% yield) and **17** (0.4 mg, 5% yield). The undesired **17** could be converted into **16** by the same protocol (treatment with 5% HCl in MeOH for 12 h).

Compound **16**: colorless crystals; mp 184−186 °C (*n*-hexane−EtOAc); IR (KBr) cm^{-1} 1716, 1655, 1616; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.00 (s, 3H, 2-Me), 1.17−1.33 (m, 2H), 1.56−1.73 (m, 3H), 1.84−2.04 (m, 4H), 2.10 (m, 1H), 2.24−2.34 (m, 3H), 2.33 (d, J = 17.3 Hz, 1H, 3-C*H*H), 2.53 (m, 1H), 2.55 (d, J = 17.3 Hz, 1H, 3-CH*H*), 2.73 (m, 1H), 3.68 (s, 3H, OMe), 5.35 (d, J = 2.1 Hz, 1H, C=CH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 17.8, 20.6, 29.9, 32.9, 33.5, 33.7, 35.7, 39.4, 40.1, 40.5, 48.2, 49.0, 49.3, 55.7, 100.7, 175.1, 200.2, 214.0; MS (EI) *m*/*z* 288 (M^+); HRMS (EI) calcd for $C_{18}H_{24}O_3$ 288.1726, found 288.1726. Anal. Calcd for $C_{18}H_{24}O_3 \cdot {}^1/_7H_2O$: C, 74.31; H, 8.41. Found: C, 74.32; H, 8.32.

Compound **17**: colorless oil; IR (KBr) cm^{-1} 1716, 1650, 1598; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H, 2-Me), 1.18−1.40 (m, 2H), 1.49−1.71 (m, 3H), 1.83−2.11 (m, 5H), 2.23−2.31 (m, 2H), 2.26 (d, J = 15.9 Hz, 1H, 3-C*H*H), 2.47 (d, J = 15.9 Hz, 1H, 3-CH*H*), 2.56 (m, 1H), 2.74 (m, 1H), 2.81 (m, 1H), 3.69 (s, 3H, OMe), 5.35 (d, J = 3.0 Hz, 1H, C=CH); MS (EI) *m*/*z* 288 (M^+).

(±)-19-Nor-stemod-3-en-2-one (18) and Its C-13 Epimer (19). To a stirred mixture of **16** (12 mg, 0.035 mmol) and $LiClO_4$ (19 mg, 0.18 mmol) in Et_2O (0.5 mL) was added dropwise MeLi (1.4 M in *n*-hexane; 0.26 mL, 0.36 mmol) at −78 °C, and the mixture was stirred for 2 h. After the mixture was warmed to −20 °C, Et_2O (5 mL) and MeOH (0.5 mL) were successively added. The mixture was made acidic with 10% HCl, and saturated $NaHCO_3$ was added to the mixture. The whole was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. The concentrate was purified by preparative TLC (2:1 $CHCl_3$/EtOAc) to give **18** (7.1 mg, 59%) and **19** (2.3 mg, 19%).

Compound **18**: colorless crystals; mp 175−177 °C (*n*-hexane−EtOAc); IR (KBr) cm^{-1} 3430, 1666; ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.94 (s, 3H, 10-Me), 1.14 (s, 3H, 13-Me), 1.24−1.40 (m, 6H), 1.56 (ddd, J = 12.6, 12.6, 6.0 Hz, 1H), 1.66 (ddd, J = 12.6, 12.6, 6.0 Hz, 1H), 1.72−1.85 (m, 5H), 1.90 (s, 3H, 4-Me), 1.96−2.05 (m, 2H), 2.33 (d, J = 15.5 Hz, 1H, 1-C*H*H), 2.53 (d, J = 15.5 Hz, 1H, 1-CH*H*), 2.60 (m, 1H), 5.89 (m, 1H, C=CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.7, 22.8, 22.9, 27.9, 28.3, 30.6, 32.6, 35.2, 36.3, 38.0, 41.8, 44.2, 45.9, 48.3, 48.7, 72.2, 126.4, 163.5, 199.7; MS (EI) m/z 288 (M^+, 49), 270 (100), 217 (61), 135 (86), 121 (99); HRMS (EI) calcd for $C_{19}H_{28}O_2$ 288.2088, found 304.2400. Anal. Calcd for $C_{19}H_{28}O_2 \cdot {}^1/_5H_2O$: C, 78.15; H, 9.80. Found: C, 78.21; H, 9.49.

Compound **19**: colorless crystals; mp 125−127 °C (*n*-hexane−EtOAc); IR (KBr) cm^{-1} 3426, 1666; ^1H NMR ($CDCl_3$, 270 MHz) δ: 0.94 (s, 3H, 10-Me), 1.24 (s, 3H, 13-Me), 1.24−1.88 (m, 13 H), 1.90 (s, 3H, 4-Me), 1.98 (m, 1H), 2.20 (m, 1H), 2.36 (d, J = 15.5 Hz, 1H, 1-C*H*H), 2.47 (d, J = 15.5 Hz, 1H, 1-CH*H*), 2.55 (m, 1H), 5.89 (m, 1H, C=CH); MS (EI) m/z 288 (M^+); HRMS (EI) calcd for $C_{19}H_{28}O_2$ 288.2088, found 288.2084.

(±)-Stemodinone (2). To a stirred suspension of CuI (30 mg, 0.16 mmol) in Et_2O (1 mL) was added MeLi (1.4 M in *n*-hexane, 0.23 mL, 0.32 mmol) at −78 °C, and the stirring was continued for 10 min at 0 °C. TMSCl (0.1 mL, 0.79 mmol) in Et_2O (0.5 mL) was added at −78 °C, and the mixture was stirred for 6 min. Solutions of **18** (9.4 mg, 33 mmol) in Et_2O (1 mL) and HMPA (0.14 mL, 0.80 mmol) in Et_2O (0.5 mL) were successively added to the above reagent. After the mixture was stirred for 1 h with warming to −20 °C, a solution of Et_3N (0.2 mL) in Et_2O (0.5 mL) was added to the mixture at −78 °C. Saturated $NaHCO_3$ (0.5 mL) was added to the mixture, and the mixture was stirred at room temperature. After NH_4Cl (0.5 mL) was added to the mixture, the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The concentrate was purified by column chromatography (1:1 $CHCl_3$/EtOAc) to give **2** (2.5 mg, 25% yield) and recovered **18** (6.6 mg, 70%). (±)-Stemodinone **2**: colorless crystals; mp 203−205 °C (*n*-hexane−CH_2Cl_2; lit. 199−201 °C);[9a] IR (KBr) cm^{-1} 3399, 1691; ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.93 (s, 3H), 0.97 (s, 3H), 1.09 (s, 3H), 1.13 (s, 3H), 1.20−1.40 (m, 6H), 1.47−1.54 (m, 2H), 1.72−1.85 (m, 6H), 1.96−2.02 (m, 2H), 2.10 (dd, J = 12.8, 2.6 Hz, 1H), 2.32 (dd, J = 12.1, 2.4 Hz, 1H), 2.34 (d, J = 12.8 Hz, 1H), 2.44 (d, J = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.8, 22.6, 23.9, 27.9, 28.3, 30.4, 32.7, 34.5, 36.1, 37.3, 38.2, 39.2, 44.8, 45.9, 47.3, 50.2, 51.5, 56.0, 72.2, 212.4; MS (EI) m/z 304 (M^+, 12.2), 233 (100), 149 (62), 133 (69); HRMS (EI) calcd for $C_{20}H_{32}O_2$ 304.2401, found 304.2400.

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Supporting Information Available: ^1H NMR spectra of compounds **2**, **7a**,**b**, **8**, **9**, **12**, **13**, and **16**−**19** as well as ^{13}C NMR spectra of compounds **2**, **7a**, **8**, **9**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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