Synthetic Studies toward the Bicyclic Peroxylactone Core of Plakortolides

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Abstract: En route to the synthesis of plakortolide E and I, we prepared a β-hydroperoxy vinyl epoxide, obtained from (*R*)-epichlorhydrin in 13 steps and 30% yield, via chemoselective methylenation with Nysted reagent in the presence of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ and regioselective Mukaiyama–Isayama hydroperoxysilylation. Unexpectedly, acid-catalyzed cyclization of this peroxy epoxide occurred exclusively through a 5-*exo* mode to furnish a 1,2-dioxolane; this is in contrast to the behavior of hydroxy analogues.

Key words: cyclization, endoperoxides, hydroperoxysilylation, plakortolides

Marine sponges of genus *Plakortis* and *Plakinastrella* are a prolific source of cyclic peroxides, many of which exhibit antifungal, antitumor, and antiparasitic activities.[1] The majority of these natural products contain six-membered peroxide structure (1,2-dioxane). Plakortolides, one of the family of secondary metabolites found in these sponges, have an aromatic unit connected via a methylene chain to a bicyclic 4,6-dimethyl peroxylactone ring system.[2] They differ in absolute and relative configuration at C-3, C-4, C-6, the substitution pattern, the level of unsaturation, and of the chain length. A representative sample of plakortolides is depicted in Figure 1.

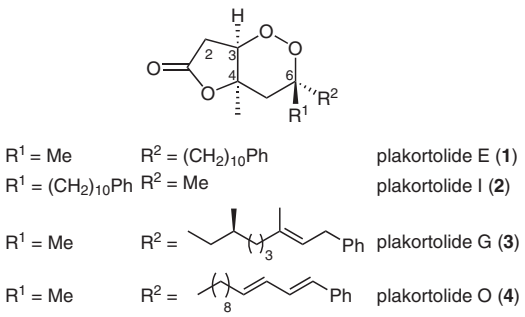
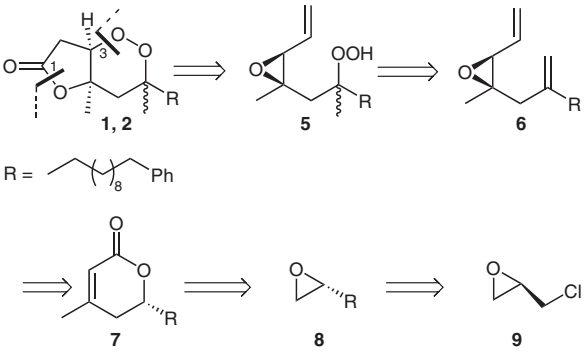


Figure 1 Representatives examples of plakortolides

A survey of the literature showed only one racemic synthesis of a member of plakortolides: plakortolide I (**2**) has been reported.[3] [4+2] Photocycloaddition of singlet oxygen to a diene and iodolactonization are the key steps for the construction of the peroxylactone framework of plakortolide I. A drawback of this strategy is the lack of stereochemical control at the newly formed stereogenic centers.

In connection with our interest in exploiting the directing effect of a double bond in the regiocontrol of intramolecular cyclization of hydroxy epoxides via disfavored 5- or 6-*endo*-tet modes according to Baldwin's rules,[4] to prepare substituted furans or pyrans,[5] we wondered if this concept could be applied to the synthesis of 1,2-dioxanes by cyclization of β-hydroperoxy vinyl epoxides. There are only few examples in the literature for the formation of a 1,2-dioxane ring system by cyclization of hydroperoxy epoxides.[6] This strategy of 1,2-dioxane ring forming has been successfully applied to the synthesis of natural-product-containing endoperoxides such as yingzhaosu C[6b] and dihydroplakortin.[6d,e] In all cases, the cyclization proceeded via a 6-*exo* mode following Baldwin' rules.

The feasibility of our approach to the 4,6-dimethylperoxylactone framework of plakortolides, based on *anti*-Baldwin cyclization of β-hydroperoxy vinylepoxides, was tested on the structurally most simple plakortolides: plakortolides E (**1**)[7] and I (**2**). These two compounds were isolated in minute amounts ($3{\cdot}10^{-4}$% for **2**) from the sponge *plakortis sp*.[2c,h] Plakortolide E (**1**) has potent and selective activity against melanoma and breast tumor cell lines ($LC_{50} < 1$ μM);[2c] no biological activity has been reported for **2**.



Scheme 1 Retrosynthetic analysis of plakortolide E (**1**) and plakortolide I (**2**)

In the retrosynthetic analysis of **1** and **2** (Scheme 1), we took into account the low stability of the O–O bond ($\Delta H_f = -33$ kcal/mol for 1,2-dioxane)[8] and its susceptibility to reducing agents as well as nucleophiles and bases (Scheme 1).[9] Obviously, the hydroperoxide functionality has to be introduced at the late stage of the synthesis.

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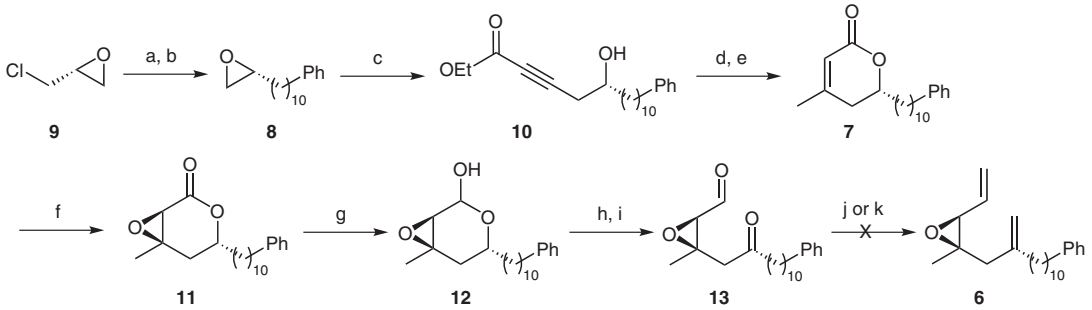


Scheme 2 *Reagents and conditions*: (a) $Ph(CH_2)_9MgBr$ (1.3 equiv), CuCN (0.1 equiv), THF, –78 °C, 2 h; (b) NaOH (5 equiv), THF, r.t., 4 h, 79% for 2 steps; (c) ethyl propiolate (3 equiv), THF, –90 °C, *n*-BuLi (3 equiv), 20 min, $BF_3{\cdot}OEt_2$ (3 equiv) then **8**, –78 °C to r.t., 98%; (d) Me_2CuLi (3 equiv) then **10**, THF, –78 °C, 0.5 h; (e) PTSA (0.1 equiv), MeOH, r.t., 4 h, 84% for 2 steps; (f) H_2O_2 (30%, 3.5 equiv), NaOH (6 N, 0.6 equiv), MeOH, 0 °C to r.t., 3 h, 82%; (g) DIBAL-H (1.1 equiv), toluene, –78 °C, 0.5 h, quant.; (h) $NaBH_4$ (2 equiv), EtOH, r.t., 4 h, 95%; (i) $(COCl)_2$ (8 equiv), DMSO (16 equiv), CH_2Cl_2, –78 °C, 1 h, then Et_3N (16 equiv), 50%; (j) $CH_2{=}PPh_3$, THF, –78 °C to r.t.; (k) $CpTiMe_2$ (4 equiv), toluene, 80 °C, 6 h.

Among the different existing methods to incorporate the hydroperoxide group, we chose the hydroperoxysilylation of alkenes developed by Mukaiyama and Isayama.[10] This cobalt-mediated reductive oxygenation of double bonds is a particularly mild and regioselective method[10a,11] which can be effected in the presence of a large number of functional groups.[6b,d,e,12] Disconnection of C_3–O and C_1–O within **1** and **2**, guided by our strategy of 6-*endo* ring closing of hydroperoxy epoxide directed by a vinyl group (a synthetic equivalent of a carboxymethyl group), revealed the vinyl epoxide **5**,which itself could arise from the epoxy diene **6** via regioselective hydroperoxysilylation. Epoxide **6** could originate from the unsaturated lactone **7** by a diastereoselective epoxidation after conventional functional adjustments. We believed intermediate **7** could be prepared from commercially available (*R*)-epichlorohydrin (**9**) via epoxide **8**.

Synthesis of plakortolides **1** and **2** commenced by a copper-catalyzed epoxide ring opening of (*R*)-epichlorohydrin (**9**) with (9-phenylnonyl)magnesium bromide[13] followed by treatment of the resulting chlorohydrin with NaOH to give the epoxide **8** in 79% yield (Scheme 2). Compound **8** was regioselectively opened with the lithium salt of ethyl propiolate, in the presence of $BF_3{\cdot}OEt_2$,[14] to provide the secondary alcohol **10** in nearly quantitative yield. Stereoselective addition of lithium dimethylcuprate[15] to the triple bond and subsequent lactonization of the resulting *Z*-enoate with *p*-toluenesulfonic acid in methanol at room temperature furnished the lactone **7** in 84% overall yield. Exposure of **7** to alkaline hydrogen peroxide in methanol gave the epoxide **11**, as a single diastereomer, in 82% yield. This *trans*-selective epoxidation of pentenolides is well precedented.[16] After DIBAL-H reduction of **11** to lactol **12**, the stage was now set up to introduce the double bond in the α-position to the oxirane functionality. In order to attain this goal, reduction of the lactol **12** with $NaBH_4$ followed by Swern oxidation provided the ketoaldehyde **13** in 47% overall yield. Unfortunately, in the presence of an excess of methylenetriphenylphosphorane or Petasis reagent,[17] compound **13** led exclusively to decomposition.

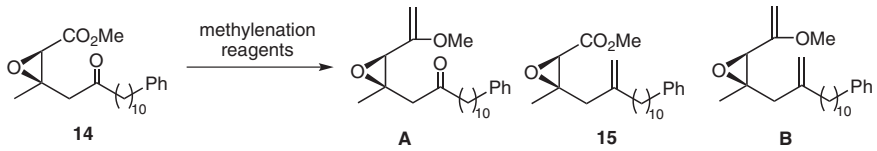
A new strategy was devised to introduce the two double bonds in a stepwise manner and was based on the ability of titanium carbenoid reagents to effect, under mild conditions, chemoselective methylenation of ketones in the presence of esters[18] (Scheme 3). A one-pot saponification of the lactone function of **11** followed by RuO_4 oxidation[19] of the resulting hydroxy sodium carboxylate gave, after diazomethane esterification, the keto ester **14** in nearly quantitative yield. Monomethylenation of **14** turned out to be somewhat troublesome as seen in Table 1.

In the presence of methylene triphenylphosphorane or using the Lombardo protocol,[20] only polar products were formed (Table 1, entries 1, 2). In the latter case, Ti(III) present in the reaction medium is known to act as a reducing agent to form pinacol-type byproducts.[21] In the presence of the Tebbe reagent, compound **14** gave **15** in low yield (Table 1, entry 3).[22]

Exposure of **14** to Petasis reagent and its catalyzed version[23] afforded about a 1:1 mixture of mono- and dimethylenation products (Table 1, entries 4, 5). Next, we turned our attention to another *gem*-bimetallic reagent: the Nysted reagent.[24] Thus, keto ester **14**, treated with Nysted reagent and $TiCl_4$, afforded **15** in a low yield due to decomposition (Table 1, entry 6). The use of an equal mixture of $TiCl_4$ and $Ti(i\text{-}OPr)_4$[21] in combination with Nysted reagent improved considerably the yield of **15** (Table 1, entry 7).[25] Having attained our challenging target, its transformation to **6** was effected in 83% yield via standard functional manipulations.

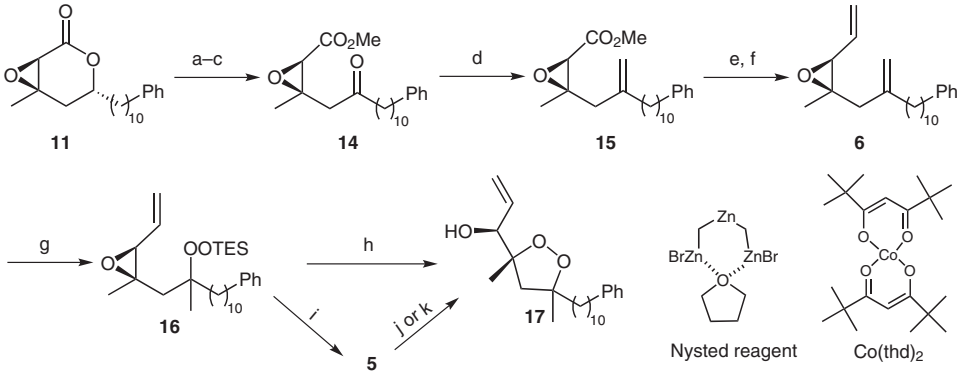
The stage was thus set for the chemoselective peroxidation of epoxydiene **6**. The best results, in terms of yield and chemoselectivity, were obtained by reaction of **6** with oxygen and triethysilane in dichloroethane, in the presence of bis[2,2,6,6-tetramethylheptane-3,5-dienoate Co(II)] $[Co(thd)_2]$[11] and by stopping the reaction at about 80% of conversion in order to avoid the bisperoxidation. The unseparable mixture of **6** and **16**, purified through a short pad of silica gel for removing the catalyst, was treated with strongly acidic resin Amberlyst-15 which effected cleavage of the TES group and concomitant cyclization to afford exclusively the 5-*exo*-cyclized product **17** in 51%

Table 1 Study of the Regioselective Methylenation of Keto Ester **14**



Entry	Reagents	Temp (°C)	Time (h)	Yield of **14** (%)[a]	Yield of **A** (%)	Yield of **15** (%)	Yield of **B** (%)
1	$Ph_3P{=}CH_2$	–78 to r.t.	3	–[b]	–	–	–
2	Zn, CH_2Br_2, $TiCl_4$	0 to r.t.	4	–[b]	–	–	–
3	$Cp_2TiClCH_2AlMe_2$	–78 to r.t.	14	–	–	23	–
4	Cp_2TiMe_2	80	21	22	3[c]	34	41
5	Cp_2TiMe_2, Cp_2TiCl_2 cat.	80	6	21	3[c]	31	27
6	$TiCl_4$, Nysted reagent	0 to 15	1	–	–	35	–
7	**$Ti(Oi\text{-}Pr)_2Cl_2$, Nysted reagent**	**0 to 15**	**0.25**	**15**	**–**	**70**	**–**

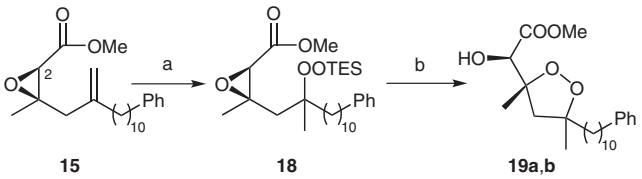
[a] Isolated yield.
[b] Only decomposition was observed.
[c] Determined by ^1H NMR.



Scheme 3 *Reagents and conditions*: (a) NaOH (2 equiv), MeOH, r.t., 2 h, then evaporation in vacuo; (b) $RuCl_3$ (0.05 equiv), $NaIO_4$ (3 equiv), K_2CO_3 (2 equiv), H_2O, r.t., 2–3 h; (c) CH_2N_2 (1.2 equiv), Et_2O, r.t., 10 min, 96% for 3 steps; (d) Nysted reagent (3 equiv), $Ti(Oi\text{-}Pr)_2Cl_2$ (2.5 equiv), THF, 0–15 °C, 15–20 min, 70%; (e) DIBAL-H (5 equiv), toluene, –78 °C, 40 min; (f) Ph_3PMeBr (5 equiv), *n*-BuLi (4 equiv), THF, 0 °C then aldehyde, 30 min, 83% for 2 steps; (g) $Co(thd)_2$ (0.1 equiv), O_2 (1 atm), Et_3SiH (1.2 equiv), DCE, r.t., silica gel filtration, 80% conversion (% determined by ^1H NMR); (h) Amberlyst-15 (0.5 equiv), CH_2Cl_2, r.t., 3 h, 51% from **6**; (i) TBAF (1.3 equiv), THF, r.t., 0.5 h; (j) Amberlyst-15 (0.5 equiv), CH_2Cl_2, r.t., 3 h, 17% from **6**; (k) HCl (12 M, 6 equiv), MeCN, r.t., 5 h, 30% from **6**.

yield.[26] The structure of **17**, obtained as a 1:1 mixture of diastereomers, was ascertained by 2D NMR experiments (HMBC, HSQC, NOESY). A stepwise procedure for the formation of endoperoxide **17** involving the deprotection of the TES group with NBu_4F affording **5** and acid-promoted ring closure in the presence of Amberlyst-15 or 12 N HCl in acetonitrile[27] gave **17** in lower yields than in the one-pot reaction. As in literature precedents for hydroxy and protected amino vinyl-*cis*-epoxides, the *cis* configuration seems to disfavor the 6-*endo* ring closure perhaps because these systems cannot assume the planar arrangement necessary for maximum stabilization in the transition state, perhaps because of steric interactions.[28]

Finally, we tested another strategy based on the expectations that a peroxy anion derived from a δ-hydroperoxy epoxy ester such as **18** should undergo a cylization at the less hindered and more electrophilic position of the oxirane, namely at the C-2 position (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) $Co(thd)_2$ (0.1 equiv), O_2 (1 atm), Et_3SiH (2 equiv), DCE, r.t., 3–4 h, 86%; b) K_2CO_3 (0.3 equiv), MeOH, 0 °C, 3 h, 75%.

Regioselective hydroperoxysilylation of the *gem*-disubstituted olefin of **15** under Mukaiyama and Isayama con-

ditions yielded a 1:1 diastereomeric mixture of the triethylsilylperoxy ester **18** in 86% yield. Treatment of **18** with a catalytic amount of potassium carbonate gave, after TES cleavage, again exclusively a 1,2-dioxolane derivative: **19a**,**b**, obtained in a good yield as a mixture of diastereomers, separable by preparative TLC. Compounds **19** are structurally closely related to plakinic acids of general formula **20** (Figure 2). These natural products, isolated from sponges of the family Plakinidae, display cytotoxicity against fungal and cancer cell lines.[2e,h,29]

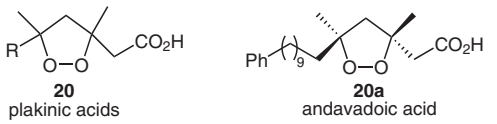


Figure 2

In summary, during the study of plakortolide synthesis we have shown that cyclization of β-hydroperoxy vinyl-*cis*-epoxides occurred only via a 5-*exo* mode, unlike hydroxy analogues, to give 1,2-dioxolanes. In this case, the vinyl group has no directing effect. We also described a modification of the method of methylenation of Matsubara et al., using Nysted reagent and a mixture of $TiCl_4$ and Ti(*i*-OPr)$_4$, which allowed the chemoselective methylenation of a keto ester in the presence of sensitive functional groups such as epoxides. Extension of the Mukaiyama and Isayama peroxygenation method to the diene **6** allowed the introduction of the hydroperoxide function regio- and chemoselectively. Finally, cyclization of hydroperoxy keto ester **18** furnished 3,5-dimethyl-1,2-dioxolane ester, structure closely related to plakinic acid natural product family **20**. Studies are under way in our laboratories to apply this strategy to the synthesis of some of these members such as andavadoic acid (**20a**).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) (a) Casteel, A. N. *Nat. Prod. Rep.* **1999**, *16*, 55. (b) Rahm, F.; Hayes, P. Y.; Kitching, W. *Heterocycles* **2004**, 523.
(2) (a) Davidson, B. S. *Tetrahedron Lett.* **1992**, *32*, 7167. (b) Horton, P. A.; Longley, R. E.; Kelly-Borges, M.; McConnell, O. J.; Ballas, L. M. *J. Nat. Prod.* **1994**, *57*, 1374. (c) Varoglu, M.; Peters, B. M.; Crews, P. *J. Nat. Prod.* **1995**, *58*, 27. (d) Qureshi, A.; Salva, J.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **1998**, *61*, 1539. (e) Williams, D. E.; Allen, T. M.; Van Soest, R.; Behrisch, H. W.; Andersen, R. J. *J. Nat. Prod.* **2001**, *64*, 281. (f) Perry, T. L.; Dickerson, A.; Khan, A. A.; Kondru, R. K.; Beratan, D. N.; Wipf, P.; Kelly, M.; Hamann, M. T. *Tetrahedron* **2001**, *57*, 1483. (g) Chen, Y.; Killday, K. B.; McCarthy, P. J.; Schemoler, R.; Chilson, K.; Selitrennikoff, C.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **2001**, *64*, 262. (h) Rudi, A.; Afanii, R.; Gravalos, L. G.; Aknin, M.; Gaydou, E.; Vacelet, J.; Kashman, Y. *J. Nat. Prod.* **2003**, *66*, 682. (i) Jimenez-Romero, C.; Ortiz, I.; Vincente, J.; Vera, B.; Rodrigue, A. D.; Nam, S.; Jove, R. *J. Nat. Prod.* **2010**, *73*, 1694. (j) Yong, K. W. L.; De Voss, J. J.; Hooper, J. N. A.; Garson, M. J. *J. Nat. Prod.* **2011**, *74*, 194.
(3) Jung, M.; Ham, J.; Song, J. *Org. Lett.* **2002**, *4*, 2763.
(4) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(5) Doan, H. D.; Gallon, J.; Piou, A.; Vatèle, J.-M. *Synlett* **2007**, 983.
(6) (a) Porter, N. A.; Funk, M. O.; Gilmore, D.; Isaac, R.; Nixon, J. *J. Am. Soc.* **1976**, *98*, 6000. (b) Xu, X.-X.; Dong, H.-Q. *J. Org. Chem.* **1995**, *60*, 3039. (c) Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. *Tetrahedron Lett.* **1997**, *38*, 8753. (d) Gemma, S.; Marti, F.; Gabellieri, E.; Campiani, G.; Novellino, E.; Butini, S. *Tetrahedron Lett.* **2009**, *50*, 5719. (e) Gemma, S.; Gabellieri, E.; Coccone, S. S.; Marti, F.; Taglialatela-Scafati, O.; Novellino, E.; Campiani, G.; Butini, S. *J. Org. Chem.* **2010**, *75*, 2333.
(7) In a recent paper on the isolation and structure elucidation of new plakortolides, Yong et al.[2j] compared the NMR data of newly isolated plakortolides and plakortolide E. They noted inconsistencies between the reported structure of plakortolide E and of its ^{1}H NMR and ^{13}C NMR data.[2c] They suggested that these data are those of seco-plakortolide E.
(8) Hay, T. S.; Yamada, T.; Tsai, P. L.; Buzzelli, J. W. *J. Phys. Chem. A* **1997**, *101*, 2471.
(9) (a) Saito, L.; Nittala, S. S. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, **1983**, 311. (b) Dussault, P. H.; Eary, C. T.; Woller, K. R. *J. Org. Chem.* **1999**, *64*, 1789. (c) Szpilman, A. M.; Korshin, E. E.; Hoss, R.; Posner, G. H.; Bachi, M. D. *J. Org. Chem.* **2001**, *66*, 6531. (d) Jin, H.-X.; Liu, H.-H.; Zhang, Q.; Wu, Y. *J. Org. Chem.* **2005**, *70*, 4240. (e) Griesbeck, A. G.; Cho, M. *Tetrahedron Lett.* **2009**, *50*, 121.
(10) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573. (b) Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1305.
(11) O'Neill, P. M.; Hindley, S.; Pugh, M. D.; Davies, J.; Bray, P. G.; Park, B. K.; Kapu, D. S.; Ward, S. A.; Stocks, P. A. *Tetrahedron Lett.* **2003**, *44*, 8135.
(12) (a) Oh, C. H.; Kim, H. J.; Wu, S. H.; Won, H. S. *Tetrahedron Lett.* **1999**, *40*, 8391. (b) Tokuyasu, T.; Kunikawa, S.; McCullough, K. J.; Masuyama, A.; Nojima, M. *J. Org. Chem.* **2005**, *70*, 251. (c) Silva, E. M. P.; Pye, R. J.; Cardin, C.; Harwood, L. M. *Synlett* **2010**, 509.
(13) Görgen, G.; Boland, W.; Preiss, U.; Simon, H. *Helv. Chim. Acta* **1989**, *72*, 917.
(14) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(15) Corey, E. J.; Katzenellenbogen, J. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
(16) For examples of substituted pentenolide epoxidation, see: (a) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539. (b) Yadav, V. K.; Kapoor, K. K. *Tetrahedron* **1995**, *51*, 8573. (c) Reddy, M. V. R.; Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **2001**, *624*, 239. (d) Sawant, K. B.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 7911. (e) Ding, J.; Jennings, M. P. *J. Org. Chem.* **2008**, *73*, 5965.
(17) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(18) For a review on titanium carbenoid reagents, see: Hartley, R. C.; Li, J.; Main, C. A.; McKierran, G. J. *Tetrahedron* **2007**, *63*, 4825.

(19) Lee, D. G.; Congson, L. N.; Spitzer, U. A.; Olson, M. E. *Can. J. Chem.* **1984**, *62*, 1835; and references cited therein.
(20) (a) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. (b) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.
(21) Okazoe, K.; Hibino, J.-I.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5581.
(22) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
(23) For Cp_2TiCl_2-catalyzed methylenation with Petasis reagent, see: Payak, J. F.; Huffman, M. A.; Cai, D.; Hughes, D. L.; Collins, P. C.; Johnson, B. K.; Cottrell, I. F.; Tuma, L. D. *Org. Process Res. Dev.* **2004**, *8*, 256.
(24) (a) Tochtermann, W.; Bruhn, S.; Meints, M.; Wolff, C.; Peters, E. M.; von Schnering, H. G. *Tetrahedron* **1995**, *51*, 1623. (b) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313.
(25) **Procedure for the Chemoselective Methylenation of Compound 14**
To a stirred solution of ketone **14** (0.219 g, 0.585 mmol) in dry THF (8 mL) was added Nysted reagent (20% in THF, 3.51 mL, 1.83 mmol), purchased from Aldrich, at 0 °C under N_2 atmosphere followed by dropwise addition of $TiCl_2(O\textit{i}\text{-}Pr)_2$ (2. 5 equiv), prepared from $TiCl_4$ (1 M in CH_2Cl_2; 0.73 mL, 0.73 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (0.217 mL, 0.73 mmol). The reaction mixture was then allowed to reach 15 °C and stirred for 15 min. The reaction mixture was cooled to 0 °C, treated carefully with H_2O (1 mL) and extracted with Et_2O (5 × 8 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution and brine. The ethereal solution was filtered through a small pad of silica gel to remove metal species, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (Et_2O–PE, 1:5) to furnish **15** (0.153 g, 70%) as a colorless oil; $[\alpha]_D^{20}$ –29.2 (*c* 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (br, m, 14 H), 1.38 (s, 3 H), 1.60 (m, 2 H), 1.95 (m, 2 H), 2.35 (d, *J* = 15 Hz, 1 H), 2.41 (d, *J* = 15 Hz, 1 H), 2.59 (t, *J* = 8.1 Hz, 2 H), 3.37 (s, 1 H), 3.76 (s, 3 H), 4.79 (s, 1 H), 4.85 (s, 1 H), 7.16–7.29 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 27.6, 29.4–29.7 (6C), 31.6, 36.1, 36.3, 39.0, 52.3, 59.0, 62.2, 112.2, 125.6, 128.3 (2 C), 128.5 (2 C), 143.0, 145.3, 169.0. IR (neat): 1646, 1736, 1757, 2854, 2927, 3026 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{24}H_{36}NaO_3$ $[MNa]^+$: 395.2557; found: 395.2557.
(26) No 6-*endo* product was detected by ^1H NMR of the crude mixture.
(27) For the use of these acid conditions in the 6-*endo* cyclization of epoxy alcohols, see: Chapelat, J.; Buss, A.; Chougnet, A.; Woggon, W.-D. *Org. Lett.* **2008**, *10*, 5123.
(28) (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (b) Ha, J. D.; Shin, E. Y.; Chung, Y.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1567.
(29) (a) Davidson, B. S. *J. Org. Chem.* **1991**, *56*, 6722. (b) Chen, Y.; McCarthy, P. J.; Harmody, D. K.; Schimoler-O'Rourke, R.; Chilson, K.; Selitrennikoff, C.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **2002**, *65*, 1509.