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Versatile 8-Oxabicyclo[3.2.1]oct-6-en-3-one: Stereoselective Methodology for Generating *C*-Glycosides, *δ*-Valerolactones, and Polyacetate Segments

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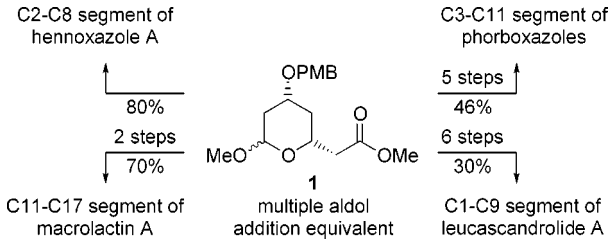
ABSTRACT



A new rearrangement of functionalized methoxy glycosides and a regioselective as well as stereoselective intramolecular Michael addition giving *δ*-valerolactones and *C*-glycosides are described. Applications to the synthesis of marine natural products are reported. Chemoselective deprotection of benzylated hydroxy groups is assumed to be facilitated by 6-*endo-tet* interaction with the 1,3-dithiane functionality.

Marine natural products are of much current interest because of their challenging stereochemistry and their high bioactivity. In preceding papers we have targeted prominent polyoxygenated marine metabolites using our oxabicyclic concept with the aim of developing a unified synthetic strategy.[1] We now exemplify our approach with the synthesis of the C11−C17 segment of macrolactin A,[2] the C3−C11 segment of the phorboxazoles,[3] the C1−C9 segment of leucascandrolide A,[4] and the C2−C8 segment of hennoxazole A[5] from a single precursor (Scheme 1).

These various polyketide segments are of the simple polyacetate type,[6] the stereocontrolled synthesis of which is generally more challenging than that of polypropionates. Our strategy is outlined in Scheme 1. The segments are cyclic and of the tetrahydropyran type (phorboxazoles, leucascandrolide A, and hennoxazole A) and also acyclic as in macrolactin A.

As starting material we chose 8-oxabicylo[3.2.1]oct-6-en-3-one **2**, which has to be elaborated into a suitable six-membered ring ether and also into a polyol chain. The key intermediate is methoxy acetal **1**,[7] in which the oxygenation pattern and stereochemistry are already placed correctly for the task at hand. Methoxy acetal **1** is a multiple aldol addition equivalent and available in high chemical yield and enantio-

(1) (a) Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883 and references therein. (b) Misske, A. M.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 3313.

(2) (a) Isolation: Gustafson, K.; Roman, M.; Fenical, W. *J. Am. Chem. Soc.* **1989**, *111*, 7519. (b) Stereochemical determination: Rychnovsky, S. D.; Skalitzky, D. J.; Pathirana, C.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **1992**, *114*, 671. (c) Total syntheses: Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095. (d) Kim, Y.; Singer, R. A.; Carreira, E. M. *Angew. Chem.* **1998**, *110*, 1321; *Angew. Chem., Int. Ed.* **1998**, *37*, 1261.

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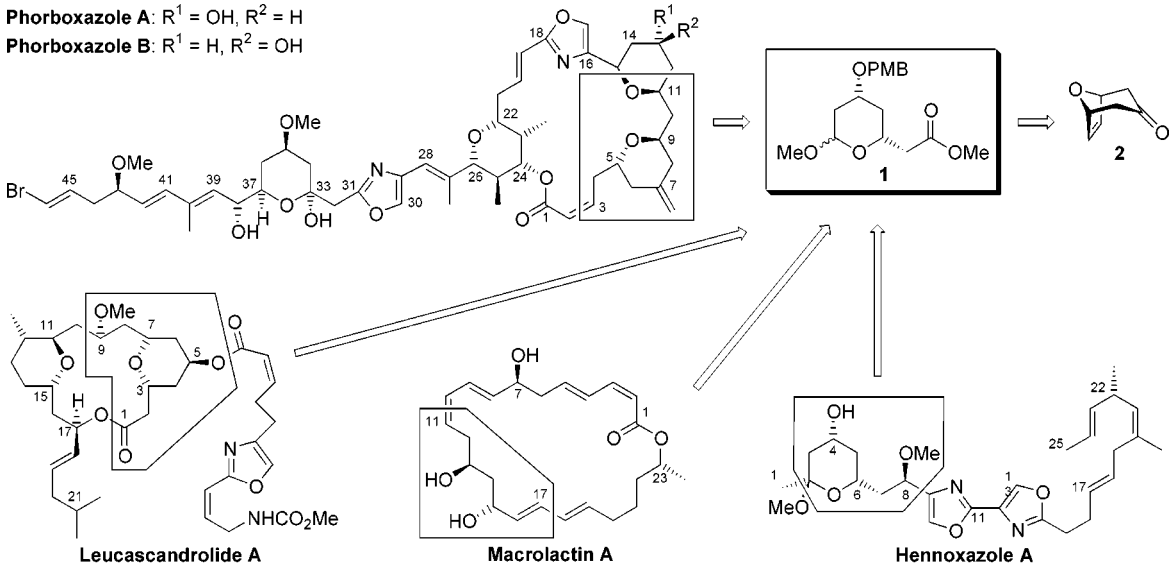
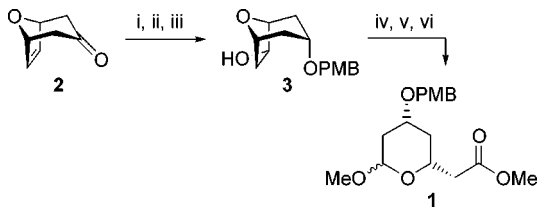
Scheme 1



meric purity from σ-symmetric title compound **2** (Scheme 2).[8]

Scheme 2[a]



[a] Reagents and conditions: (i) L-Selectride, perfusor, THF, −78 °C, 1 h, 82%; (ii) NaH, PMBCl, Bu_4NI, THF, reflux, 6 h, 85%; (iii) (+)-Ipc_2BH, THF, −10 °C, 1 week, 85%, 96% ee; (iv) PCC, CH_2Cl_2, rt, 5 h, 92%; (v), *m*-CPBA, CH_2Cl_2, rt, overnight, 96%; (vi) MeOH, concentrated H_2SO_4 (catal.), rt, overnight, 91%.

The opening of methoxy acetals related to **1** has been described previously.[9] We chose the PMB protecting group to facilitate simultaneous deprotection[7a,10] of the masked hydroxy function. We discovered that the deprotective opening in solvents more polar than dichloromethane is feasible with $BF_3{\cdot}Et_2O$ and 1,3-propanedithiol. Loss of the PMB group is thought to be facilitated by 1,6-intramolecular nucleophilic interaction of 1,3-dithiane sulfur (6-*endo*-*tet*, see Table 1, ***i***). In a structurally related case we found that debenzylation also occurred with ease. Acyclic diol **4** and functionalized δ-valerolactone **5** are formed in one step in a single-flask reaction (Table 1). The opening and deprotection worked best in acetonitrile. The conditions chosen (entry 5) favored formation of lactone **5**. After aqueous workup, cyclization to the desired lactone **5** was completed by addition of PPTS in CH_2Cl_2 (Table 1, footnote b). $BF_3{\cdot}Et_2O$ (1.1 equiv) also promotes the equilibration of **4** to **5**, without destroying diol ester **4**.

At first sight the cascade **1** → **5** would seem to correspond to no less than five classical steps: (i) reduction at C1 to aldehyde, (ii) protection as thioacetal, (iii) deprotection at

(3) (a) Isolation and structure determination: Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879. (d) Total Syntheses of phorboxazoles: Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem.* **2000**, *112*, 2633; *Angew. Chem., Int. Ed.* **2000**, *39*, 2533. (e) Evans, D. A.; Fitch, D. M. *Angew. Chem.* **2000**, *112*, 2636; *Angew. Chem., Int. Ed.* **2000**, *39*, 2536. (f) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597.

(4) (a) Isolation and structure determination: Ambrosio, M. D.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51. (b) Synthetic effort: Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597.

(5) (a) Isolation and structure: Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173. (b) Higa, T.; Tanaka, J.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227. (c) Total syntheses: Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157 (including stereochemical determination). (d) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924.

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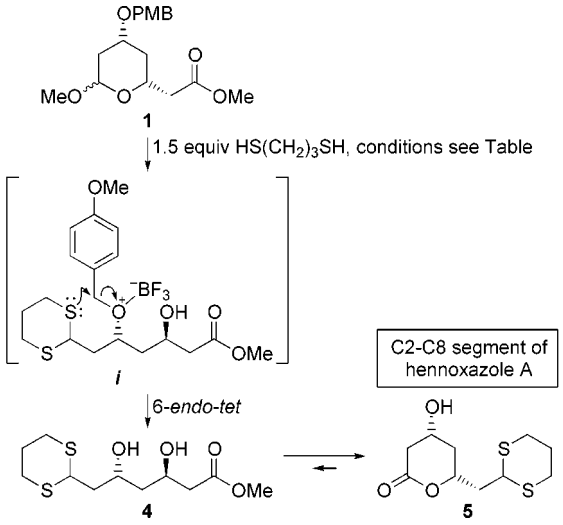
(7) (a) Wolbers, P.; Hoffmann, H. M. R.*Tetrahedron* **1999**, *55*, 1905. (b) Dunkel, R.; Mentzel, M.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 14929.

(8) Kim, H.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **2000**, 2195 and references therein.

(9) For some examples, see: (a) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (b) Lampe, T. F. J.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.* **1996**, 1931. (c) Nakata, T.; Nagao, S.; Takao, S.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 73. (d) Nakata, T.; Nagao, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 75. (e) Nakata, T.; Takao, S.; Fukui, M.; Takana, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 3873.

(10) Deprotection of the benzyl group: (a) $BF_3{\cdot}Et_2O$/EtSH: Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661. (b) $BF_3{\cdot}Et_2O$/NaI: Vankar, Y. D.; Rao, C. T. *J. Chem. Res., Synop.* **1985**, 232.

Table 1. Cascade Lactonization of Methoxy Acetal **1**



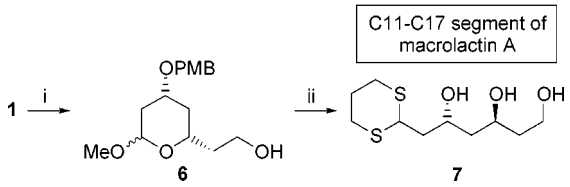
entry	BF_3·Et_2O [equiv]	conditions	ratio **4**:**5** (TLC analysis)[a]	isolated yield of **5** [%]
1	5	$MeNO_2$, −20 °C → rt, 2 h	1:5	31
2	7	MeCN, −20 °C → rt, 4 h	1:5	41
3	4.5	MeCN, −20 °C → rt, 4 h; then TFA (5 equiv), rt, 20 min	1:6	50
4	3	MeCN, −20 °C → 0 ° C, 1 h	1:1	61[b]
5	1.1	MeCN 0 °C, 0.5 h	1:9	80[b]

[a] Before aqueous workup. [b] Aqueous workup, then PPTS (0.5 equiv), CH_2Cl_2, rt, 1 h, and column chromatography.

C5, (iv) deprotection at C7, and (v) oxidation at C7. Owing to the hidden C_2 symmetry of acyclic intermediates, the termini of **5** and **1** are simply interchanged and are fully differentiated with *umpolung* of one terminus. Lactone **5**, more so than methoxy acetal **1**, is a suitable precursor of the C2−C8 segment of hennoxazole A.

To obtain the acyclic building block from **1**, the cyclization **4** → **5** was stopped by simply reducing the ester terminus (**1** → **6**, Scheme 3). Ring opening of acetal **6** by our protocol

Scheme 3. Polyol **7** from Methoxy Acetal **1**[a]

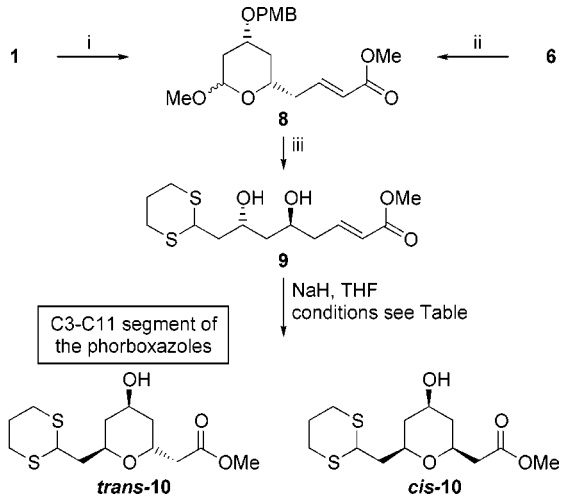


[a] Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C to rt, 1 h, 99%; (ii) 1.3 equiv $HS(CH_2)_3SH$, 4.5 equiv of BF_3·Et_2O, MeCN, −20 °C to rt, 2.5 h, 71%.

afforded the acyclic polyketide **7** of macrolactin A, again with *umpolung* of polarity of one terminus.

As a further reaction mode of methoxy acetal **1**, we homologated the ester to α,β-unsaturated ester **8** by Wittig methodology (Table 2). Alternatively, ester **8** was obtained

Table 2. Two-Carbon Homologation to α,β-Unsaturated Esters **8** and **9**. Cyclization to THP Building Blocks ***trans*-10** and ***cis*-10**



[a]

entry	NaH [equiv]	conditions	yield [%]	***trans*-10**:***cis*-10**[b]
1	4.3	−60 °C, 1.5 h; −5 °C, 2 h	45	52:48
2	3.0	−78 °C, 1 h; −25 °C, 22 h	56	68:32
3	3.0	−78 °C → 0 °C, 3 h	48	80:20
4	2.5	−60 °C → −5 °C, 6 h; −5 °C, 2 h	74	75:25
5	2.2	−78 °C → −5 °C, 1 h; −5 °C, 15 h	50	57:43
6	**2.2**	**−78 °C → 0 °C, 2.5 h**	**78**	**81:19**
7	2.1	−78 °C → rt, 3 h; rt, 3 h	20	2:98
8	1.0	−40 °C → rt, 1 h; rt, 15 h	25	2:98
9	**1.0**	**−40 °C → rt, 1 h; rt, 7 h**	**61**	**2:98**
10	0.2	rt, 8 h	90	60:40

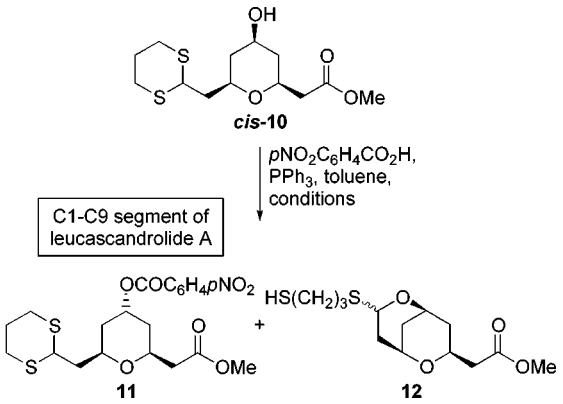
[a] (i) DIBAH, CH_2Cl_2, 0.5 h, −78 °C, then Ph_3PCHCO_2Me, 16 h, rt, 73%; (ii) 1. Dess−Martin periodinane, CH_2Cl_2, 1 h, 0 °C, 87%; 2. Ph_3PCHCO_2Me, CH_2Cl_2, rt, 18 h, 98%; (iii) 1.5 equiv of $HS(CH_2)_3SH$, 1.3 equiv of BF_3·Et_2O, MeCN, 0 °C → rt, 0.5 h, 70%. [b] The relative configuration at the new stereocenter was confirmed by NOE experiments.

by the three-step sequence **1** → **6** → **8** (84% overall yield). Ring opening dithioketalization of **8** was accompanied by deprotection of the PMB group, giving diol **9** without subsequent cyclization. Further investigations afforded *C*-glycosidic tetrahydropyrans containing three individual stereocenters. Either ***trans*-10** (entry 6, Table 3) or predominantly ***cis*-10**[11] (entry 9) was obtained under basic[12] Michael-type conditions.[13] All-equatorial ***cis*-10** is assumed to be the stereoisomer of thermodynamic control.

Mitsunobu inversion[14] of alcohol ***cis*-10** usually occurred with intervention of the dithioacetal group, giving bicyclic *O*,*S*-acetal **12**.[15] The conditions of entry 5 provided the

(11) Acid-induced cyclization appears to give poorer *cis*:*trans* ratios: Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727.

Table 3. Mitsunobu Reaction of Alcohol ***cis*-10** in the Presence of a Dithiane Moiety



entry	PPh_3 [equiv]	conditions	yield **11** + **12** [%]
1	1.6	1.6 equiv of DIAD, rt, 4 h	42 + 31
2	5	1.6 equiv of DIAD, rt, 3 h	51 + 23
3	10	2.0 equiv of DEAD, rt, 3 h	80 + 9
4	10	1.6 equiv of DBAD, rt, 5 h	64 + n.d.[a]
5	14	2.0 equiv of DEAD, rt, 1 h	85 + 0

[a] Not determined.

desired ester **11** in good yield (85%). Steric encumbrance of azoester (DEAD, DIAD, DBAD) did not improve the formation of **11**. Tetrahydropyrans ***trans*-10** and **11** serve as the C3−C11 segment of the phorboxazoles and as the C1−C9 segment of leucascandrolide A, respectively.

In summary, oxabicyclic precursor **2** and anomeric methoxy acetal **1** are universal polyacetate building blocks. Two deceptively simple seven-carbon segments, **5** and **7**, as well as three fully differentiated nine-carbon polyacetate segments, ***trans*-10**, ***cis*-10**,[16] and **11**, have been synthesized by efficient chemistry and in high enantiomeric purity. All building blocks can be used in the synthesis of marine natural products.

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Supporting Information Available: Experimental procedures and spectroscopic data of the compounds **5**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The role of double bond geometry in controlling the diastereoselectivity in this type of Michael addition: Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 967.

(14) Modification of the Mitsunobu protocol for inversion of sterically hindered secondary alcohols using *p*-nitrobenzoic acid: Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(15) The excess of PPh_3 is assumed to suppress nucleophilic attack of dithiane on DEAD and subsequent ring opening of 1,3-dithiane.

(16) (a) C11−C19 segment of 17-deoxyroflamycoin: Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. (b) *C*-Glycoside unit of the hydrangenosides A−G: Uesato, S.; Takeda, Y.; Hashimoto, T.; Uobe, K.; Inouye, H.; Taguchi, H.; Endo, T. *Helv. Chim. Acta* **1984**, *67*, 2111 and references therein.