Synthesis of (tetrahydrofuranyl)tetrahydrofurans *via* radical cyclization of bis(β-alkoxyacrylates)

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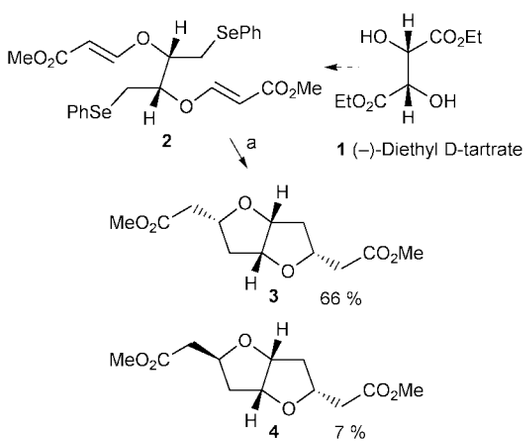
Radical cyclizations of bis(β-alkoxyacrylates) obtained from (3*R*,4*R*)- and *meso*-1,6-dibromohexane-3,4-diol proceed to form a C_2-symmetric and a *meso* (tetrahydrofuranyl)tetrahydrofuran derivative.

β-Alkoxyacrylates are excellent precursors for stereoselective preparation of *cis*-2,5-substituted tetrahydrofurans and *cis*-2,6-substituted tetrahydropyrans *via* radical cyclizations.[1] Fused oxacycles may be prepared from double cyclizations; radical cyclizations of the bis(β-alkoxyacrylate) **2** obtained from (2*S*,3*S*)-1,4-bis(phenylseleno)butane-2,3-diol led to the formation of the *cis*-fused C_2-symmetric 2,6-dioxabicyclo[3.3.0]-octane derivative **3**,[2] which served as a key intermediate in the formal total synthesis of (−)-kumausallene (Scheme 1).[3] Aside

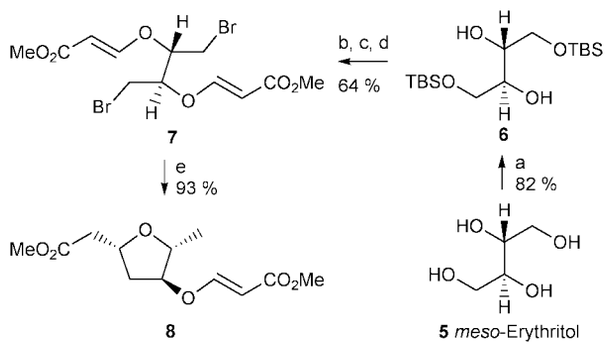


Scheme 1 a) 2.5 eq. Bu_3SnH, 0.25 eq. AIBN, benzene (0.02 M), reflux, 5 h (syringe pump, 4 h).

from its ascetic beauty, we were intrigued by the efficacy of the double radical cyclization strategy for fused oxacycles like **3**, which called for further investigations.

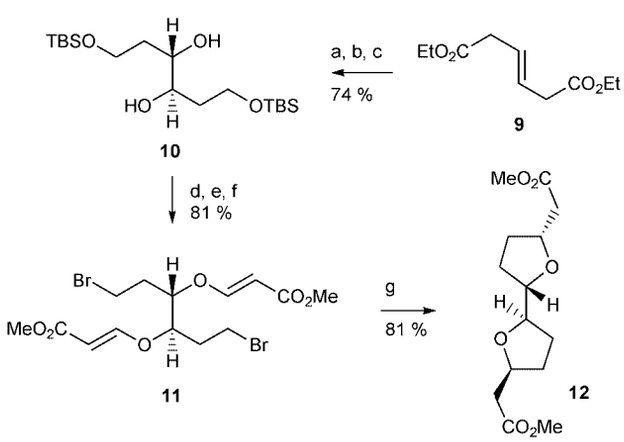
meso-Erythritol (**5**) served as the starting point in the attempted synthesis of the *trans*-fused *meso* isomer of **3**. The diol **6** was obtained *via* selective TBS protection of the primary hydroxy groups of **5**, which was then converted into the corresponding bis(β-alkoxyacrylate). Deprotection of the TBS groups and primary bromide substitution with carbon tetrabromide–triphenylphosphine led to the formation of the bis-(β-alkoxyacrylate) **7**. When the substrate **7** was allowed to react with tributylstannane under high dilution conditions, a high yield of the tetrahydrofuranyl product **8**[4] was obtained. Apparently, thermodynamic bias against the *trans*-fused bicyclo-[3.3.0]octane systems prevented the second radical cyclization step necessary for the bicycle formation (Scheme 2).

We then turned our attention to the bishomo analogues of the substrates **2** and **7**. Diethyl *trans*-hex-3-enedioate (**9**) was reduced with lithium aluminium hydride, and the resulting *trans*-hex-3-ene-1,6-diol was converted into the epoxide, from which the *meso* diol **10** was obtained *via* aqueous acid treatment and TBS protection of the 1,6-hydroxy groups. The bis(β-



Scheme 2 a) TBSCl, imidazole, cat. DMAP, DMF, r.t. 1 h; b) $HCCCO_2Me$, *N*-methylmorpholine (NMM), DCM, r.t. 4 h; c) conc. HCl, MeOH, r.t. 30 min; d) CBr_4, Ph_3P, DCM, r.t. 30 min; e) 2.4 eq. Bu_3SnH, 0.2 eq. AIBN, benzene (0.025 M), reflux, 5 h (syringe pump, 4 h).

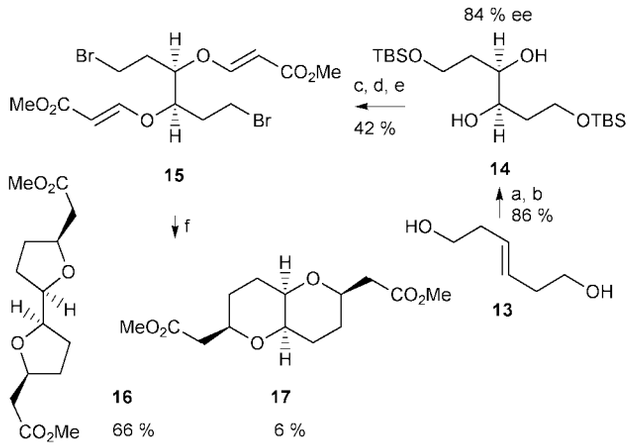
alkoxyacrylate) **11** was obtained following the known three step sequence of reactions from **10**, and it was transformed into the *meso*-(tetrahydrofuranyl)tetrahydrofuran derivative **12**[5] in high yield under the standard conditions (Scheme 3). The pre-



Scheme 3 a) LAH, ether, 0 °C; b) MCPBA, DCM, 0 °C, 1 h; aq. H_2SO_4, r.t. 12 h; c) TBSCl, imidazole, DMF, r.t. 30 min; d) $HCCCO_2Me$, NMM, DCM, r.t. 3 h; e) conc. HCl, MeOH, r.t. 10 min; f) CBr_4, Ph_3P, DCM, r.t. 1 h; g) 2.4 eq. Bu_3SnH, 0.2 eq. AIBN, benzene (0.025 M), reflux, 5 h (syringe pump, 4 h).

dominant formation[6] of the product **12** attests to the complete dominance of the 5-*exo* mode of radical cyclization over the alternative 6-*exo* mode, which would have generated a (tetrahydropyrano)tetrahydropyran product.

Next, *trans*-hex-3-ene-1,6-diol (**13**) was converted into the bis(TBS) ether, and it was subjected to the Sharpless asymmetric dihydroxylation conditions to provide the diol **14** in 84% ee.[7] The preparation of the bis(β-alkoxyacrylate) **15** from **14** proceeded without incident. When the substrate **15** was allowed to react with tributylstannane under high dilution



Scheme 4 a) TBSCl, imidazole, DCM; b) AD-mix-β, $MeSO_2NH_2$, $NaHCO_3$, *t*-BuOH–H_2O (1 : 1), 0 °C; c) $HCCCO_2Me$, NMM, DCM, r.t.; d) conc. HCl, MeOH, r.t.; e) CBr_4, Ph_3P, DCM, r.t.; f) 2.4 eq. Bu_3SnH, 0.2 eq. AIBN, benzene (0.025 M), reflux, 5 h (syringe pump, 4 h).

conditions, the C_2-symmetric (tetrahydrofuranyl)tetrahydrofuran **16**[8] and the C_2-symmetric (tetrahydropyrano)tetrahydropyran **17**[9] were obtained in 66% and 6% yield, respectively (Scheme 4). In this case, the 6-*exo* cyclization competes with the favored 5-*exo* cyclization, albeit ineffectively.

The present results show that radical cyclization strategy may provide an effective alternative in the synthesis of multi-oxacyclic motifs of current interest.[10] Further efforts in these laboratories towards synthesis of oxacyclic natural products and functional molecular systems will be reported in due course.

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Notes and references

1 (*a*) E. Lee, J. S. Tae, C. Lee and C. M. Park, *Tetrahedron Lett.*, 1993, **34**, 4831; (*b*) E. Lee, J. S. Tae, Y. H. Chong, Y. C. Park, M. Yun and S. Kim, *Tetrahedron Lett.*, 1994, **35**, 129; (*c*) E. Lee and C. M. Park, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 293; (*d*) E. Lee, J.-w. Jeong and Y. Yu, *Tetrahedron Lett.*, 1997, **38**, 7765; (*e*) E. Lee, C. M. Park and J. S. Yun, *J. Am. Chem. Soc.*, 1995, **117**, 8017; (*f*) E. Lee, S.-K. Yoo, Y.-S. Cho, H.-S. Cheon and Y. H. Chong, *Tetrahedron Lett.*, 1997, **38**, 7757.

2 In this case, a small amount of the minor product **4** was also obtained.

3 E. Lee, S.-K. Yoo, H. Choo and H. Y. Song, *Tetrahedron Lett.*, 1998, **39**, 317.

4 ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.28 (d, 3H, J = 6.5 Hz), 1.90–1.95 (m, 1H), 2.17–2.19 (dd, 1H, J = 5.4, 1.6 Hz), 2.55 and 2.68 (AB of ABX, J_{AB} = 15.6 Hz, J_{AX} = 6.7 Hz, J_{BX} = 6.1 Hz), 3.70 (s, 6H), 4.06–4.09 (m, 1H), 4.40 (m, 1H), 4.50 (m, 1H), 5.17 (d, 1H, J = 12.7 Hz), 7.51 (d, 1H, J = 12.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.69, 37.54, 39.98, 51.18, 51.78, 74.33, 79.83, 86.18, 97.81, 160.70, 167.87, 171.06; MS (EI, relative intensity) 258 (M^+, 3), 157 (86), 83 (100).

5 ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.56–1.66 (m, 2H), 1.73–1.83 (m, 2H), 1.91–2.11 (m, 4H), 2.47 and 2.61 (AB of ABX, J_{AB} = 15.2 Hz, J_{AX} = 6.9 Hz, J_{BX} = 6.4 Hz), 3.68 (s, 6H), 3.80–3.86 (m, 2H), 4.24–4.33 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.59, 30.79, 40.68, 51.55, 75.70, 81.34, 171.63; MS (CI, relative intensity) 287 (M+1, 100), 255 (26), 213 (20); HRMS (CI) calcd for $C_{14}H_{23}O_6$ 287.1495, found 287.1493.

6 A trace amount of a minor (presumably epimeric) product was obtained.

7 Sharpless asymmetric dihydroxylation of *trans*-1,6-dibromohex-3-ene, obtained from *trans*-hex-3-ene-1,6-diol *via* mesylation and bromide substitution, provided 74% yield of (3*R*,4*R*)-1,6-dibromohexane-3,4-diol in high enantiomeric excess (>98%). Reaction of this diol with ethyl propiolate was a little sluggish, and gave 40% yield of the corresponding bis(β-alkoxyacrylate). Radical cyclization produced ethyl ester analogues of **16** and **17** in 72% and 6% yield, respectively.

8 $[a]_D^{28}$ −8.9 (*c* 1.8, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.56–1.78 (m, 4H), 1.86–1.96 (m, 2H), 2.01–2.12 (m, 2H), 2.47 and 2.73 (AB of ABX, J_{AB} = 15.4 Hz, J_{AX} = 6.3 Hz, J_{BX} = 7.2 Hz), 3.68 (s, 6H), 3.80–3.87 (m, 2H), 4.25–4.34 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.59, 30.94, 40.48, 51.50, 75.78, 81.55, 171.68; MS (CI, relative intensity) 287 (M + 1, 100), 255 (86), 213 (21); HRMS (CI) calcd for $C_{14}H_{23}O_6$ 287.1495, found 287.1499.

9 $[a]_D^{26}$ −14.9 (*c* 0.62, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.32–1.44 (m, 2H), 1.54–1.71 (m, 4H), 1.84–1.94 (m, 2H), 2.41 and 2.58 (AB of ABX, J_{AB} = 15.3 Hz, J_{AX} = 7.3 Hz, J_{BX} = 5.7 Hz), 3.39 (br, 2H), 3.71 (s, 6H), 3.74–3.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.69, 29.17, 41.29, 51.56, 71.34, 73.82, 171.97; MS (CI, relative intensity) 287 (M + 1, 77), 255 (100), 213 (34); HRMS (CI) calcd for $C_{14}H_{23}O_6$ 287.1495, found 287.1491.

10 (*a*) U. Koert, *Synthesis*, 1995, 115; (*b*) Many of the more recent references on the synthesis of Annonaceous acetogenins may be found in A. Sinha, S. C. Sinha, S. C. Sinha and E. Keinan, *J. Org. Chem.*, 1999, **64**, 2381.

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