Pure & Appl. Chem., Vol. 68, No. 3, pp. 631–634, 1996.
Printed in Great Britain.

Oxacycle synthesis via radical cyclization of β-alkoxyacrylates

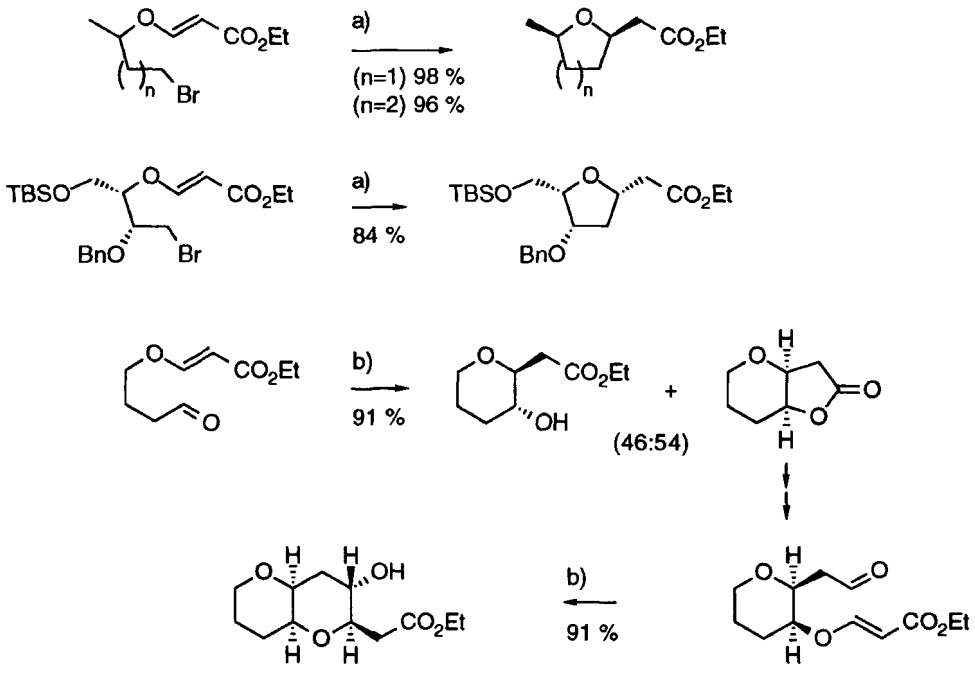
Eun Lee

Department of Chemistry, College of Natural Sciences, Seoul National University
Seoul 151-742, Korea

Abstract: (Tetrahydrofuran-2-yl) and (tetrahydropyran-2-yl)acetates are efficiently synthesized via radical cyclization of β-alkoxyacrylates. Facile synthesis of marine natural products (*3Z*)- and (*3E*)-dactomelyne is achieved.

Preliminary Studies

Use of β-alkoxyacrylates[1] as radical acceptors results in the efficient formation of (tetrahydrofuran-2-yl) and (tetrahydropyran-2-yl)acetates.[2,3] The reactions are highly stereoselective: *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans are formed exclusively when substrates derived from secondary alcohols are employed. With aldehydic substrates, cyclization is again very efficient, but stereoisomeric mixtures of products resulted, although the *cis* stereochemistry of 2,5- and 2,6-disubstitution is retained.[4] Fused oxacycle formation is possible by employing the reactions reiteratively. (Scheme 1)



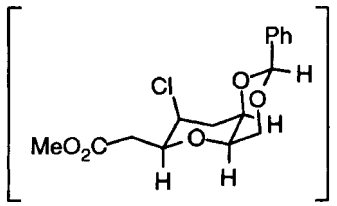
a) 1.2 eq. Bu_3SnH, 0.25 eq. AIBN, Benzene (0.03 M), Reflux, 6 h, (Syringe Pump, 5 h)
b) 1.3 eq. Bu_3SnH, 0.25 eq. AIBN, Benzene (0.03 M), Reflux, 8 h

Scheme 1

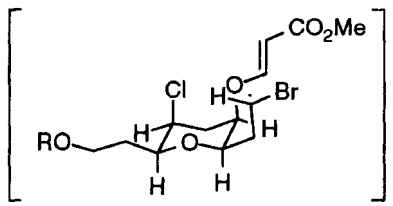
Synthesis of Dactomelynes

(*3Z*)- and (*3E*)-Dactomelyne were isolated from digestive glands of the sea hare *Aplysia dactylomela* and they possess the fused pyranopyran skeleton.[5] Chlorine and bromine substitutions at the β-carbons are the most characteristic features in their structures. Stereoselective introduction of the halogen atoms in the ring systems is difficult, as manifested in an unsuccessful attempt for the systhesis of these marine natural products.[6]

Our interest in dactomelynes derived from the fact that they exhibit dual *cis* 2,6-disubstituted pyran motif. We were confident that the construction of the pyranopyran skeleton could be achieved via two independent radical cyclization reactions of β-alkoxyacrylate substrates prepared ultimately from (-)-diethyl D-tartrate (**9**). The cyclization products were expected to possess (methoxycarbonyl)methyl groups of correct orientation, from which the ethyl and 2-penten-4-ynyl substituents would be elaborated. The stereoselective introduction of halogen atoms required more careful analysis. The trichloro substrate **7** should be transformed into the dichloro bicyclic product **6**, from which the chloro derivative **5** would be obtained via stereoselective radical dehalogenation via the intermediate radical **10**. Finally, radical cyclization of the dibromo substrate **4** should lead to the pyranopyran product **3**. In the intermediate radical **11**, the bromo substituent was expected to stay away from steric congestion. It is noteworthy that in both of these reactions, steric bias of the *cis*-fused *bicyclic* intermediate and transition state was to be utilized for maximal stereoselection.



10

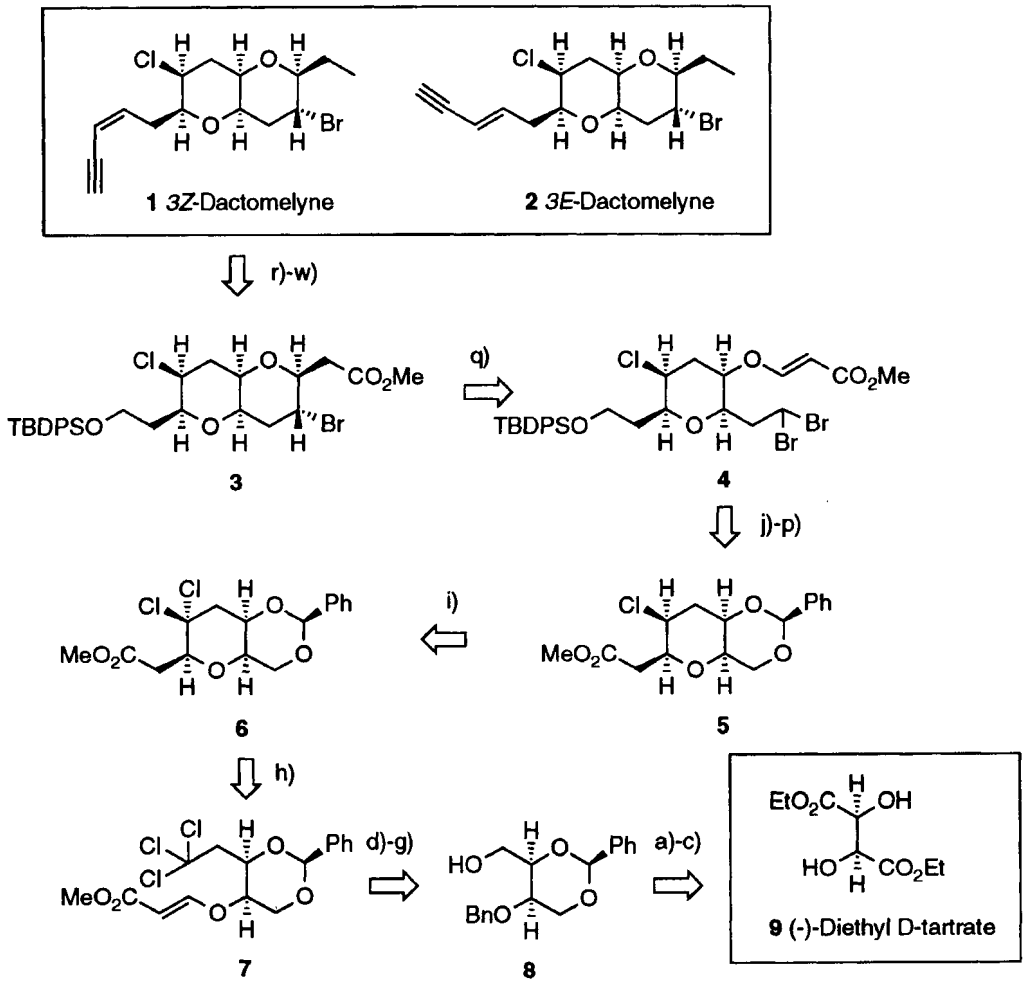


11

In the event, the cyclic acetal **8** was prepared from **9** via the known intermediates. The corresponding triflate was reacted with excess trichloromethyllithium at -110°C in the presence of HMPA to yield the trichloro product in 60% yield. Hydrogenolysis was achieved uneventfully to give the alcohol, which was converted into the β-alkoxyacrylate **7** in an excellent yield. The reaction of **7** with slight excess of tricyclohexylstannane under high dilution conditions led to the isolation of the bicyclic products in high yield. For stereoselective dechlorination of the dichloro product **6**, a variety of reagents and conditions were examined. Eventually, reaction of **6** with one equivalent of tris(trimethylsilyl)silane at room temperature in the presence of triethylborane produced 13:1 mixture of **5** and the epimer in 91% yield.

Lithium aluminum hydride reduction of **5** and subsequent t-butyldiphenylsilyl protection afforded the silyl ether, which was selectively reduced to the primary alcohol. The nitrile was obtained via the triflate derivative, and the reduction with alane led to the production of the homologous primary amine. The reaction of the primary amine with cupric bromide and t-butyl nitrite at room temperature led to the isolation of the dibromo derivative in 64% yield, which was selectively deprotected to give the alcohol. The β-Alkoxyacrylate was again efficiently produced from the alcohol. Under standard high dilution conditions with tributylstannane and AIBN in hot benzene, the pyranopyran product **3** was obtained exclusively from **4**. Remarkably, no trace of the epimeric byproduct was found in the reaction mixture.

Elaboration of the side chain ethyl and 2-penten-4-ynyl groups was carried out uneventfully. The pyranopyran **3** was reduced with lithium aluminum hydride at low temperature to give the primary alcohol, which was converted into the product with the ethyl side chain via the corresponding iodide. Deprotection and subsequent oxidation led to the isolation of the aldehyde. Mixture of the protected enynes was produced in 68% yield upon reaction of the aldehyde with lithiated 1,3-bis(triisopropylsilyl)propyne. Deprotection with tetrabutylammonium fluoride yielded 10:1 mixture of (*3Z*)-dactomelyne **1** and (*3E*)-dactomelyne **2** in a quantitative yield. (Scheme 2)



a)1.3 eq. PhCHO, cat. p-TsOH, Benzene, Reflux b) LAH-$AlCl_3$ (1:1), Ether-DCM (1:1), Reflux, 91 % (2 steps)
c) 1.2 eq. $PhCH(OMe)_2$, cat. CSA, DCM, r.t., 83 % d) 1.2 eq. Tf_2O, 4.0 eq. Pyridine, DCM, 0°C
e) 3.0 eq. LDA, 3.5 eq. $CHCl_3$, THF-Ether-HMPA (1:1:0.2) -110°C, (0.132M), (Reverse Addition), 60 % (2 steps)
f) H_2 (1 atm), Pd/C, EtOAc, r.t., 75 % g) 1.2 eq. $HCCCO_2Et$, 1.5 eq. NMM, DCM, r.t., ≈100 %
h) 1.1 eq. c-Hex_3SnH, 0.2 eq. AIBN, Benzene (0.02 M), Reflux, (Syringe Pump, 10 h), 67 % (+17 % **5**)
i) 1.0 eq. $(TMS)_3SiH$, 0.2 eq. Et_3B, Benzene, r.t. 91 % (13:1)
j) LAH, THF, 0°C / 1.2 eq. TBDPSCl, 2.0 eq. Imidazole, cat. DMAP, DCM, r.t., 90 %
k) 3.0 eq. $Na(CN)BH_3$, 2.0 eq. $TiCl_4$, MeCN, 0°C, 93 %
l) 1.2 eq. Tf_2O, 4.0 eq. Pyridine, DCM, 0°C / 10 eq. KCN, cat. 18-c-6, MeCN, r.t., 92 %
m) LAH-H_2SO_4 (2:1), THF, 0° ~ r.t., 91 % n) 2.0 eq. $CuBr_2$, 1.5 eq. t-BuONO, MeCN, r.t., 64 %
o) 1.3 eq. BCl_3, DCM, -78°C ~ -20°C, 93 % p) 1.2 eq. $HCCCO_2Et$, 1.5 eq. NMM, DCM, r.t., 95 %
q) 1.3 eq. Bu_3SnH, 0.2 eq. AIBN, Benzene (0.02 M), Reflux , (Syringe Pump, 5 h), 75 %
r) LAH, Ether, -40°C, 98 % s) 1.5 eq. I_2, 1.5 eq. Ph_3P, 3.0 eq. Imidazole, THF, 0°C, 94 %
t) 1.2 eq. $LiEt_3BH$, THF, 0°C, 97 % u) cat. p-TsOH, MeOH, r.t. / SO_3·Pyridine, TEA, DCM-DMSO(4:1), r.t., 91 %
v) TIPSCCCHLiTIPS, THF, -78°C, (Reverse Addition), 68 % w) TBAF, THF, r.t., ≈100 % (10:1)

Scheme 2

This synthesis is characterized by stereoselective introduction of alkyl and halogen substituents around pyranopyran ring system completely in line with prediction and provides further examples for the power of radical mediated reactions in the construction of complex molecules.

ACKNOWLEDGEMENT

This research was supported by Ministry of Education and the Organic Chemistry Research Center (KOSEF). A number of students were involved in the works described here. Particularly, the author thank Mr. J. S. Tae, who initiated radical cyclization studies of β-alkoxyacrylates, and Mr. C. M. Park, who synthesized dactomelynes singlehandedly.

REFERENCES

1. Y. Araki, T. Endo, Y. Arai, M. Tanji, and Y. Ishido. *Tetrahedron Lett.* **30**, 2829 (1989).
2. E. Lee, J. S. Tae, C. Lee, and C. M. Park. *Tetrahedron Lett.* **34**, 4831 (1993).
3. E. Lee and C. M. Park. *J. Chem. Soc. Chem. Comm.* 293 (1994).
4. E. Lee, J. S. Tae, Y. H. Chong, Y. C. Park, M. Yun, and S. Kim. *Tetrahedron Lett.* **35**, 129 (1994).
5. Y. Gopichand, F. J. Schmitz, J. Shelly, A. Rahman, and D. van der Helm. *J. Org. Chem.* **46**, 5192 (1981).
6. A. P. Kozikowski and J. Lee. *J. Org. Chem.* **55**, 863 (1990).