## Communications to the Editor

## Total Synthesis of Dactomelynes<sup>†</sup>

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(3Z)- and (3E)-Dactomelynes (1 and 2, Scheme 1) were isolated from the digestive glands of the sea hare Aplysia dactylomela by Schmitz and co-workers.1 Together with elatenyne,<sup>2</sup> isolated from a sample of Laurencia elata, they represent a group of nonisoprenoid ethers which are characterized by a unique pyranopyranyl skeleton with ethyl and pentenynyl substituents. The most characteristic feature in their structures is the presence of strategically located halogen atoms on the tetrahydropyran rings. The chlorine substituent is oriented on the sterically hindered side, whereas the bromine substituent avoids steric congestion. Stereoselective introduction of the halogen atoms in the ring systems is difficult, and the lack of general synthetic methods for stereoselective halide preparation is amply manifested in an unsuccessful attempt for the synthesis of dactomelynes by Kozikowski.<sup>3</sup>

Recently, we reported the use of  $\beta$ -alkoxyacrylates<sup>4</sup> as radical acceptors resulting in the efficient formation of (tetrahydrofuran-2-yl)- and (tetrahydropyran-2-yl)acetates.<sup>5</sup> Importantly, the reactions were highly stereoselective in the absence of extraneous steric influence: cis-2,5-disubstituted tetrahydrofurans and cis-2,6-disubstituted tetrahydropyrans were formed exclusively when substrates derived from secondary alcohols were employed.<sup>6,7</sup> The stereoselectivity was explained on stereoelectronic grounds in that the s-trans conformation involving the  $O-C_{\beta}$  bond should be favored in the chair-like transition state.

Our interest in dactomelynes derived from the fact that they exhibit a 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

1989, 30, 2829.

(5) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. Tetrahedron Lett. 1993, 34, 4831

(6) Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. Tetrahedron Lett. **1994**, 35, 129. (7) Lee, E.; Park, C. M. J. Chem. Soc., Chem. Commun. 1994, 293.

(8) Reactions of halogenated alkyl radicals generated from polyhalogenated precursors are well known: (a) Walling, C.; Huyser, E. S. Org. React. (N.Y.) 1963, 13, 91. For some of the more recent examples involving (N.1.) 1903, 13, 91. For some of the more recent examples involving halogen-substituted alkyl radicals, see: (b) Wilcox, C. S.; Gaudino, J. J. Am. Chem. Soc. 1986, 108, 3102. (c) Nagai, M.; Lazor, J.; Wilcox, C. S. J. Org. Chem. 1990, 55, 3440. (d) Watanabe, Y.; Ueno, Y.; Tanaka, C.; Okawara, M.; Endo, T. Tetrahedron Lett. 1987, 28, 3953. (e) Watanabe, Y.; Endo, T. Tetrahedron Lett. 1988, 29, 321. (f) Feldman, K. S.; Berven, H. M.; Weinreb, P. H. J. Am. Chem. Soc. 1993, 115, 11364. (g) Barth, F.; O-Yang, C. Tetrahedron Lett. 1991, 32, 5873. For some of the more recent examples involving halogen-substituted  $\alpha$ -carbonylalkyl radicals, see: (h) Agashimes involving halogen-substituted u-caroonylarky radicals, see: (n)
Nagashima, H.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. Tetrahedron Lett. 1983, 24, 2395. (i) Hayes, T. K.; Villani, R.; Weinreb, S. M. J. Am. Chem. Soc. 1988, 110, 5533. (j) Sato, T.; Ishida, S.; Ishibashi, H.; Ikeda, M. J. Chem. Soc., Perkin Trans. 1 1991, 353. (k) Barth, F.; O-Yang, C. Tetrahedron Lett. 1990, 31, 1121. (l) Dowd, P.; Zhang, W. J. Am. Chem. Soc. 1992, 114, 10084. (m) Pirrung, F. O. H.; Steeman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.;
Kamphuis, L. Tetrahedron Lett. 1902, 33, 5141. (a) Kouracki, B.; Walch Kamphuis, J. Tetrahedron Lett. 1992, 33, 5141. (n) Kawecki, R.; Welch, J. T. Tetrahedron Lett. 1993, 34, 3087.

Scheme 1



of  $\beta$ -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. Employment of polyhalogenated substrates<sup>8,9</sup> for 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 by stereoselective radical dehalogenation via the intermediate radical 10. Finally, radical cyclization of the dibromo substrate 4 should lead to

(9)  $\beta$ -Alkoxyacrylate substrates carrying three and two bromine substituents were synthesized, and they were found to be efficient precursors in the tributylstannane-mediated radical cyclizations.



a) 5.0 eq. LDA, 5.2 eq. CHBr<sub>3</sub>, THF-Ether-HMPA (1:1: 0.2), -110 °C (Reverse Addition) b) Same as in a) but with 2.0 eq. LDA, 2.1 eq. CH<sub>2</sub>Br<sub>2</sub>, -90 °C c) cat. p-TSOH, MeOH, ct. d) 1.2 eq. HCCC0<sub>2</sub>Et, 1.5 eq. NMM, DCM, r.t. 1.2 eq. Bu<sub>3</sub>SnH, 0.2 eq. AlBN, Benzene (0.02M), Reflux (Syringe Pump, 5 h) f) Same as in e) but with 1.0 eq. Bu<sub>3</sub>SnH

<sup>&</sup>lt;sup>+</sup> This paper is dedicated to Professor Koji Nakanishi on the occasion of his 70th birthday.

<sup>(1)</sup> Gopichand, Y.; Schmitz, F. J.; Shelly, J.; Rahman, A.; van der Helm, Gopichand, T., Schnitz, F.J., Gheny, J., Kalana, T., J., J., Org. Chem. 1981, 46, 5192.
 Hall, J. G.; Reiss, J. A. Aust. J. Chem. 1986, 39, 1401.
 Kozikowski, A. P.; Lee, J. J. Org. Chem. 1990, 55, 863.
 Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishido, Y. Tetrahedron Lett.

Scheme 2

1) PhCHO, H<sup>+</sup>



the pyranopyran product 3. In the intermediate radical 11, the bromo substituent was expected to stay away from steric congestion (Scheme 1). It is noteworthy that, in each of these reactions, steric bias in the cis-fused bicyclic intermediate and the transition state was to be utilized for maximal stereoselection.

In the event, the cyclic acetal 8 was prepared from 9 via the known intermediates<sup>10</sup> (Scheme 2). The corresponding triflate 12 was reacted with excess (trichloromethyl)lithium<sup>11</sup> at -110°C in the presence of HMPA to yield the trichloro product 13. Hydrogenolysis was achieved uneventfully to give the alcohol, which was converted into the  $\beta$ -alkoxyacrylate 7 in an excellent yield. The reaction of 7 with a slight excess of tricyclohexylstannane under high-dilution conditions led to the isolation of the dichloro product 6 in 67% yield. The monochloro product 5 was also isolated in 17% yield, accompanied by 14 in 11% yield, as products of further reduction.<sup>12</sup> For stereoselective dechlorination, a variety of reagents and conditions were examined.<sup>13</sup> Eventually, reaction of 6 with 1 equiv of tris-(trimethylsilyl)silane<sup>14,15</sup> at room temperature in the presence of triethylborane produced a 13:1 mixture of 5 and 14 in 98% yield.

Lithium aluminum hydride reduction of 5 and subsequent tertbutyldiphenylsilyl protection afforded 15, which was selectively reduced<sup>16</sup> to the primary alcohol **16**. The corresponding nitrile was obtained via the triflate derivative of 16, and reduction with alane<sup>17</sup> led to production of the homologous primary amine **17**. The reaction of 17 with cupric bromide and tert-butyl nitrite at room temperature<sup>18</sup> led to the isolation of the dibromo derivative  $18^{19}$  in 64% yield. It was selectively deprotected to give the corresponding alcohol, from which the  $\beta$ -alkoxyacrylate 4 was again efficiently produced. Under standard high-dilution conditions with tributylstannane and AIBN in hot benzene, the pyranopyran product 3 was obtained exclusively from 4 (Scheme

(10) Al-Hakim, A. H.; Haines, A. H.; Morley, C. Synthesis 1985, 207. (11) (Trichloromethyl)lithium addition to carbonyl compounds was reported. Taguchi, H.; Yamamoto, H.; Nozaki, H. J. Am. Chem. Soc. 1974, 96. 3010.

(12) It can be concluded that there was little stereocontrol in the trialkylstannane-mediated dehalogenation of cyclic dihalide systems. This is not surprising in view of the result discussed in ref 9

(13) Reaction of  $\mathbf{6}$  with tributylstannane and AIBN in hot benzene resulted in the formation of a 1:1.6 mixture of 5 and 14 in 83% yield. Use of triphenylstannane at room temperature with triethylborane led to the isolation of a 1:1.2 mixture in 89% yield. A 1.6:1 mixture of 5 and 14 was obtained when tricyclohexylstannane was used with AIBN in hot benzene (93% yield) or with triethylborane at room temperature (96% yield).
 (14) Giese, B.; Kopping, B.; Chatgilialoglu, C. Tetrahedron Lett. 1989.

30, 681

(15) Reversal of stereoselectivity in the reduction of gem-dichlorides by tributylstannane and tris(trimethylsilyl)silane was recently reported: Apeloig, Y.; Nakash, M. J. Am. Chem. Soc. 1994, 116, 10781.
 (16) Adam, G.; Seebach, D. Synthesis 1988, 373.

 (17) Yoon, N. M.; Brown, H. C. J. Am. Chem. Soc. 1968, 90, 2927.
 (18) Doyle, M. P.; Siegfried, B. J. Chem. Soc., Chem. Commun. 1976, 433

(19) The more direct route to **18** involving the triflate of **16** and (dibromomethyl)lithium was sluggish. For the use of (dibromomethyl)-lithium, see: Villieras, J.; Bacquet, C.; Normant, J.-F. Bull. Soc. Chim. Fr. 1975, 1797.

(20) There is only a small steric bias in the formation of monocyclic products from bromo-substituted radicals as discussed in ref 9. The exclusive formation of 3 reflects complete stereocontrol via steric hindrance. Scheme 3





3). Remarkably, no trace of the epimeric byproduct was found in the reaction mixture.<sup>20</sup>

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 19 via the corresponding iodide. Deprotection of 19 and subsequent oxidation led to the isolation of the aldehyde 20. A mixture of the protected enynes 21 and 22 was produced in 68% yield upon reaction of 20 with lithiated 1,3-bis(triisopropylsilyl)propyne.<sup>21</sup> Deprotection with tetrabutylammonium fluoride yielded a 10:1 mixture of dactomelynes 1 and  $2^{22}$  in quantitative yield (Scheme 4).

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

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Supporting Information Available: Experimental details and characterization data for polyhalogenated substrates and their cyclization products (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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<sup>(21)</sup> Corey, E. J.; Rucker, C. Tetrahedron Lett. 1982, 23, 719.

<sup>(22)</sup> Spectroscopic data for the synthesis samples of dactomelynes 1 and 2 were identical with those for the natural material. We thank professor Schmitz for supplying us with 270 MHz NMR spectra for both compounds. <sup>13</sup>C NMR: 1 (benzene-d<sub>6</sub>, 125 MHz) δ 141.06, 111.12, 83.14, 82.96, 80.51, 78,77, 75.78, 70.59, 54.63, 48.05, 41.72, 36.61, 34.90, 26.73, 8.88; **2** (chloroform-*d*, 125 MHz)  $\delta$  140.97, 111.86, 82.36, 82.04, 78.41, 76.64, 75.76, 70.31, 53.96, 47.15, 41.15, 36.87, 36.51, 25.98, 8.17.