for the free phenols[5,7] (**2a**, n = 6 and 7), the difference in the distance between carbon 1 and n of the polymethylene bridge in n = 6 and 7 is 1.3 Å. Thus we can now quantify the optimum topology for this change in complexation.

NMR data (400 MHz) for **2b** (n = 9) and its Na^+ complex in solution support this conclusion.[10] While **2b** (n = 9) displays two singlets for the ArH protons (6.901 and 6.181 ppm), two singlets for the OCH_2CO protons (5.032 and 4.428 ppm) and two quadruplets for the OCH_2CH_3 protons (4.231 and 4.114 ppm, J_{AB} = 7.2 Hz), its sodium complex displays only one (or nearly so) of each of these signals (6.925 6.912 for ArH; 4.427, 4.423 for OCH_2CO; 4.346 ppm for OCH_2CH_3), which demonstrates clearly that differences in chemical shifts are not caused by substituent effects. Furthermore, with the exception of the 1 and 9 methylene protons, all the protons of the bridge appear between 1.1 and 1.3 ppm, with no signals at higher field, whereas in the Na^+ complex two pentuplets, each for two methylene groups, appear at 0.551 and 0.408 ppm. This shows that in going to 4-fold symmetry the polymethylene chain is pulled into the more shielded zone of the cavity defined by the aromatic moieties. Clearly, the free ligand has the characteristic C_2 symmetry of a distorted calix[4]arene in the cone conformation, while the Na^+ complex requires the more regular C_4 symmetry. When this arrangement is prohibited by the shorter bridges in **2b**, n = 5 and 6, cation complexation is closed down under the experimental conditions of picrate extraction.

This sharp discontinuity in complexation associated with very minor conformational restrictions induced by polymethylene bridging suggests the possibility of designing host molecules in which conformation flexing in a reversible fashion may be coupled with the selective reception and release of guest cations. This complexation of metal ions between the ether/ester groups may be related also to the complexation of a suitable host within the hydrophobic cavity and vice versa, leading to very simple models for allosteric effects.

Acknowledgment. We thank Loctite (Ireland) Ltd. for research fellowships to S.C. and E.M.C. and Deutsche Forschungsgemeinschaft (DFG) for financial support.

Supplementary Material Available: Characterization and ^1H NMR spectra for compounds **26** (n = 5-7, 9) (6 pages). Ordering information is given on any current masthead page.

(10) ^1H NMR (400 MHz) [**2b** (n = 9), $CDCl_3$] δ 6.901 (s, 4 H, ArH), 6.181 (s, 4 H, ArH), 5.032 (s, 4 H, OCH_2CO), 4.786 (d, 4 H, $ArCH_AH_BAr$, J_{AB} = 13.2 Hz), 4.428 (s, 4 H, OCH_2CO), 4.231 (q, 4 H, OCH_2CH_3, J_{AB} = 7.2 Hz), 4.114 (q, 4 H, OCH_2CH_3, J_{AB} = 7.2 Hz), 3.120 (d, 4 H, $ArCH_AH_BAr$, J_{AB} = 13.2 Hz), 2.315 (s, 6 H, $ArCH_3$), 2.05 (m, 4 H, $ArCH_2CH_2$), 1.292 (t, 6 H, OCH_2CH_3, J_{AB} = 7.2 Hz), 1.229 (t, 6 H, OCH_2CH_3, J_{AB} = 7.2 Hz), 1.25 (br m, 8 H, $CH_2CH_2CH_2$), 1.15 ppm (br m, 6 H, $CH_2CH_2CH_2$). After shaking this solution with solid NaSCN the spectrum of the Na^+ complex is obtained: δ 6.925 (s, 4 H, ArH), 6.912 (s, 4 H, ArH), 4.427 (s, 4 H, OCH_2CO), 4.423 (s, 4 H, OCH_2CO), 4.346 (q, 8 H, OCH_2CH_3, J_{AB} = 7.1 Hz), 4.168 (d, 4 H, $ArCH_AH_BAr$, J_{AB} = 12.2 Hz), 3.311 (d, 4 H, $ArCH_AH_BAr$, J_{AB} = 12.2 Hz), 2.40 (m, 4 H, $ArCH_2CH_2$), 2.084 (s, 6 H, $ArCH_3$), 1.388 (t, 12 H, OCH_2CH_3, J_{AB} = 7.1 Hz), 1.3 (br m, 6 H, $CH_2CH_2CH_2$), 0.551 (br p, 4 H, $CH_2CH_2CH_2$, J_{AB} = 7.2 Hz), 0.408 ppm (br p, 4 H, $CH_2CH_2CH_2$, J_{AB} = 7.3 Hz).

4-Siloxy-α-bromocrotonate: A New Reagent for [2 + 3] Annulation Leading to Oxygenated Cyclopentenes at Low Temperatures

Tomas Hudlicky,*[1] Nina E. Heard, and Alison Fleming

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received March 7, 1990

Summary: The lithium dienolate of 4-siloxy-2-bromocrotonate was condensed with several enones to afford silyl enol ether terminated vinylcyclopropanes, which were rearranged at low temperatures under various conditions to the corresponding oxycyclopentenes. The conditions, unoptimized yields, and the initial results regarding the stereochemical course of this new rearrangement are reported. An application of this methodology to the synthesis of highly functionalized oxygenated cyclopentanoids such as the iridoids is suggested.

Oxygenated cyclopentanes are found in such natural products as iridoids, prostaglandins, and sesquiterpenes.[2] A number of approaches to cyclopentanoid compounds have been reported,[3] including our efforts in the area of [4 + 1] and [2 + 3] annulations.[4] We considered an efficient and a general approach to oxygenated cyclopentanoids under conditions that would tolerate a higher degree of oxygenation and substitution than permitted by the currently used thermolytic rearrangements. A methodology was envisioned that would provide oxygenated cyclopentenes such as **2** by the enantiocontrolled [2 + 3] annulation of enone **3**, derived optically pure from toluene,[5] with a zwitterion such as **1** (Figure 1), provided such a synthon could be easily prepared.

A two-step procedure for the synthesis of fused cyclopentene esters of type **7** (Figure 2) has been realized via either thermolysis or nucleophilic opening rearrangements of vinylcyclopropanes **6**.[6] We now report the use of γ-

(1) Recipient of the National Institutes of Health Research Career Development Award, 1984-1989 (AI-00564).

(2) *Handbook of Naturally Occurring Compounds*; Devon, T. K., Scott, A. I., Eds.; Academic: New York, 1972; Vol. 2.

(3) For recent reviews, see: (a) Hudlicky, T.; Price, J. *Chem. Rev.* **1989**, *89*, 1467. (b) Ramaiah, M. *Synthesis* **1984**, 529. (c) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1; *Aldrichimica Acta* **1984**, *17*, 43. (d) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429.

(4) For a recent summary of the efforts in this area, see: Hudlicky, T.; RuLin, F.; Lovelace, T. C.; Reed, J. W. Synthesis of Natural Products Containing Five-membered Rings. An Evolution of General Methodology. In *Studies in Natural Products*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 1989; Vol. 3.

(5) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735.

(6) (a) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691. (b) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; Ranu, B. C.; Papadopolous, P. *Tetrahedron* **1987**, *43*, 5685. (c) Hudlicky, T.; Fleming, A.; Lovelace, T. *Tetrahedron* **1989**, *45*, 3021.

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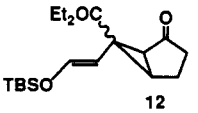
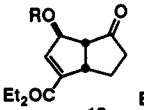
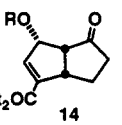
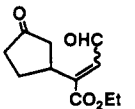
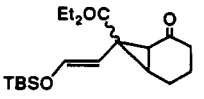
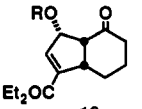
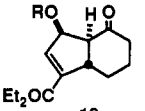
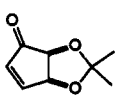
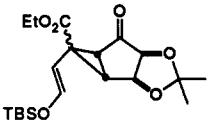
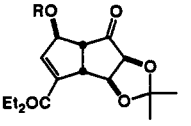
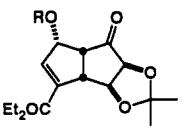
Table I. Oxycyclopentene Annulation

enone	vinylcyclopropane	reaction conditions[a]		product ratio			isolated yield, %
 11	 12			 13	 14	 15	
1.	exo or endo	A	R=TBS	1.0	2.5	0	52
2.	exo/endo	C	R=H	1.2	1.0	0	47
3.	**exo or endo**	**D**	**R=TBS**	**1.2**	**1.0**	**0**	**90**
4.	exo/endo	E	R=TBS	0	3.0	1.0	61
5.	**exo or endo**	**G**	**R=TBS**	**5.7**	**1.0**	**0**	**47**
6.	exo or endo	H	R=TBS	1.0	3.2	0	78
 16	 17				 18	 19	
7.	exo or endo	B	R=TBS		1.0	4.0	44
8.	exo/endo	C	R=H		1.0	2.3	17
9.	**exo/endo**	**D**	**R=TBS**		**0**	**1.0**	**76**
 3	 20				 2a	 2b	
10.	exo or endo	A	R=TBS		1.0	4.0	75
11.	exo or endo	F	R=H		1.0	2.0	86

[a] Reaction conditions: (A) flash vacuum pyrolysis, 550 °C (10^{-4} to 10^{-6} mmHg); (B) flash vacuum pyrolysis, 575 °C (10^{-4} to 10^{-6} mmHg); (C) 1.5 equiv of TBAF, THF, −90 °C to room temperature; (D) TMSI/HMDS, 3:1 CH_2Cl_2/pentane, −20 °C to room temperature, then $HClO_4$, aqueous THF; (E) $FeCl_3$, CH_2Cl_2, 0 °C to room temperature; (F) 2.0 equiv of TBAF, THF −40 °C, 10 min; (G) 5.0 equiv of TBAF·$3H_2O$, THF/H_2O, room temperature, 12 h; (H) 1 equiv of $ZnBr_2$, CH_2Cl_2, room temperature, 48 h.

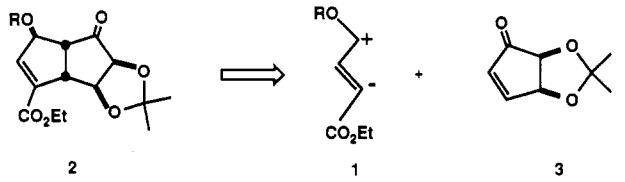


Figure 1.

oxygenated α-bromocrotonate reagent **8**, the synthetic equivalent of zwiterion **4**, whose interaction with enones leads to silyl enol ether terminated vinylcyclopropanes **9**, which rearrange to oxycyclopentanoids **10** under a variety of conditions, including low-temperature rearrangements that may be subject to charge acceleration.[7,8] In this paper we report the initial scope of this methodology and suggest its application as a means to synthesis of iridoids such as specionin.

The requisite (siloxyvinyl)cyclopropanes were prepared from enones via the addition of the lithium dienolate derived from ethyl 2-bromo-4-(*tert*-butyldimethylsiloxy)-

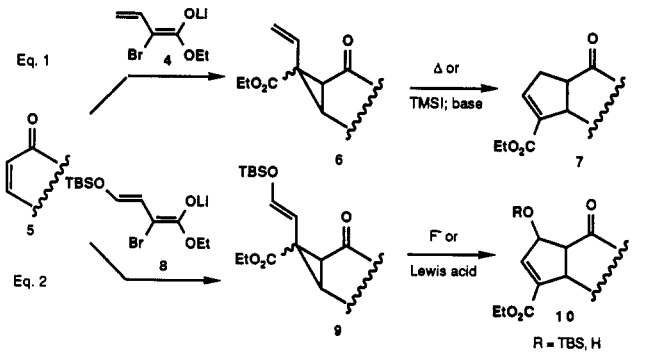


Figure 2. [2 + 3] Cyclopentene annulations.

crotonate[6a] in isolated yields ranging from 35% to 50%. (Polymerization of the dienolate anion in the unoptimized reactions accounts for the low yields. The yields are >95% when based on the consumed enone. The stoichiometry of this reaction as well as the mode of addition of the dienolate anion must be investigated and optimized.)[9] The (siloxyvinyl)cyclopropanes were obtained as mixtures (~50/50) of endo and exo isomers, separable by flash

(7) Majetich, G.; Hull, K. *Tetrahedron Lett.* **1988**, *29*, 2773.
(8) Danheiser, R. L.; Martinez-Davila, C. M.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443. (b) Danheiser, R. L.; Martinez-Davila, C. M.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340. (c) Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579. (d) Larsen, S. D. *J. Am. Chem. Soc.* **1988**, *110*, 5932.

(9) The mass balance corresponds to polymer derived from **8**. Problems similar to these were encountered also with reagent **4** and were solved by optimization of reaction conditions (inverse addition, 1.5 equiv of **4**, mixing at −100 °C). See ref 6c.

chromatography. During this study, no differences in the reactivity of the two isomers were detected.

The yields and stereoselectivity arising from the eight conditions listed in Table I were compared. Thermolyses provided the alkoxycyclopentene annulated products in 50–75% yields with the endo isomers predominating because of the endo effect.[10] Fluoride-initiated rearrangements were studied in detail to yield the optimum conditions listed in Table I,[11] which gave the highest exo/endo ratio of products when tetra-*tert*-butylammonium fluoride (TBAF)[7,12] was used. Whereas the nature of the intermediate in this rearrangement is not yet known, there may be conceptual similarities with the process recently described by Larsen[8d] in which thioenol ether terminated vinylcyclopropanes have been postulated during a low-temperature rearrangement to cyclopentenes. Trimethylsilyl iodide in the presence of hexamethyldisilazane provided the highest yields of the siloxycyclopentenes. Somewhat surprisingly, both exo and endo vinylcyclopropanes gave the siloxycyclopentenes, although our studies on vinylcyclopropanes not containing the enol ether showed that endo isomers furnished the products of divinylcyclopropane rearrangement.[6a,b] Lewis acid catalysis led predominantly to endo somers and to aldehyde **15**, which was shown *not* to be an intermediate in the reaction.

The stereochemistry of the resulting hydroxycyclopentenes was determined by protection with *tert*-butyldimethylsilyl chloride and comparison of GC and ^{1}H NMR data of their *tert*-butyldimethylsilyl ethers with those of the siloxy derivatives obtained by pyrolysis of the corresponding siloxy vinylcyclopropanes.[13] The relative percentages of exo and endo isomers were determined by integration of the ring-junction protons in ^{1}H NMR spectroscopy.[13] The endo isomers were equilibrated with TBAF at room temperature to yield a 80:20 ratio of isomers. Thus control of the stereochemistry at the oxygenated center may be available through the different conditions of this rearrangement: endo configuration from a $FeCl_3$-catalyzed reaction, exo from the fluoride-initiated rearrangement. The generality of such control is under investigation.[11]

In summary, we have described an efficient method for the annulation of oxygenated cyclopentenes that proceeds under extremely mild conditions at temperatures as low as −90 °C. At the present time, the optimum conditions (in terms of yield) for rearrangement are treatment of the vinylcyclopropane with 1.1 equiv of HMDS and TMSI at −20 °C (Table I, entry 3). This affords a 90% yield of the oxycyclopentenes with a 1.2:1.0 exo:endo ratio. The conditions leading to the most stereochemically pure product involved the use of 5 equiv of TBAF·H_2O over 12 h (Table I, entry 5, 5.7:1.0 exo:endo). The stereochemistry at the oxygenated center can be somewhat controlled by equilibration of the free alcohols with fluoride. Detailed investigations of the mechanistic course of these rearrangements, the optimization of conditions, and the conversion of intermediate **2** to (−)-specionin are in progress.[13,14]

Acknowledgment. We express our gratitude to the following agencies for their generous financial support: the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (AI-00564, AI-19749, GM-40648), and the Jeffress Trust Fund.

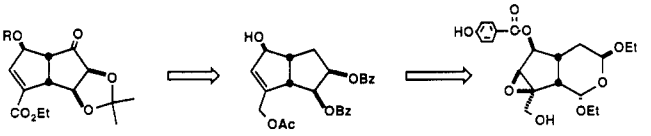
(10) RajanBabu, T. P.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759. (b) Choi, J.; Ha, D.; Hart, D.; Lee, C.; Ramesh, S. *J. Org. Chem.* **1989**, *54*, 279. (c) Wolff, S.; Agosta, W. *J. Chem. Res. (S)* **1981**, 78. (d) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373.

(11) Full optimization of the fluoride rearrangements will be reported in the full paper, in preparation.

(12) Marino, J. P.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 1. (b) Marino, J. P.; Silveira, C.; Comasseto, J.; Petragnani, L. *J. Org. Chem.* **1987**, *52*, 4131. (c) Marino, J. P.; Ling, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 7916.

(13) All compounds were characterized by IR and ^{1}H and ^{13}C NMR spectroscopy, elemental analyses, or high-resolution mass spectrometry.

(14) The reduction of the ketone and ester functionalities in **2a** to **i** has been accomplished in three steps as of this writing.



i Specionin

For references relevant to specionin, see: (a) Chang, C. C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605. (b) Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719. Syntheses: (a) Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719. (b) Van der Eycken, E.; Callant, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 367. (c) Leonard, J.; Hussain, N. *Tetrahedron Lett.* **1987**, *28*, 4871. (d) Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280. (e) Kim, B. H.; Jacobs, P. B.; Elliott, R. L.; Curran, D. P. *Tetrahedron* **1988**, *44*, 3079.

The Preparation of *C*-Arylglycals. The Palladium-Catalyzed Coupling of 3,4,6-Tri-*O*-(*tert*-butyldimethylsilyl)-1-(tributylstannyl)-D-glucal and Aryl Bromides

Richard W. Friesen* and Claudio F. Sturino

Department of Chemistry, University of Toronto, Lash Miller Chemical Laboratories, Toronto, Ontario, Canada M5S 1A1

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Summary: The palladium-catalyzed couplings of the protected 1-(tributylstannyl)-D-glucal **1** and substituted aryl bromides provide the corresponding *C*-arylglucals **4–15** and a dimer **16** resulting from the homocoupling of **1**.

Many of the *C*-aryl glycosides that have been isolated from natural sources, such as the gilvocarcins,[1] nogalamycin,[1,2] arugomycin,[1,3] and the papulacandins,[1,4] exhibit antibiotic and/or antitumor activity. As a result, there has been a considerable effort directed toward the formation of the unique C–C bond that directly links the carbohy-

(1) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1.

(2) Wiley, P. F. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982; p 97.

(3) Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Imamura, K.; Tanabe, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1983**, *36*, 1569.

(4) Traxler, K.; Grumer, J.; Auden, J. A. J. *J. Antibiot.* **1977**, *30*, 289.

0022-3263/90/1955-2572$02.50/0