Pergamon

Tetrahedron Letters, Vol. 35, No. 36, pp. 6639-6642, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01437-X

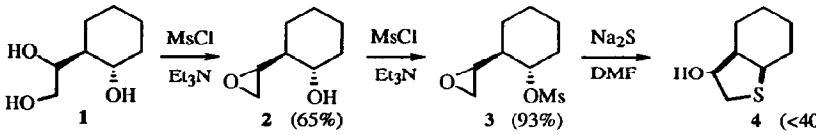
SYNTHESIS OF TETRAHYDROTHIOPHENES VIA NUCLEOPHILIC ADDITION OF HARPP'S REAGENT TO CYCLIC CARBONATES: APPLICATION TOWARD THE SYNTHESIS OF BREYNOLIDE

Russell J. Linderman*, Neil S. Cutshall, and Brian T. Becicka
Department of Chemistry, North Carolina State University
Raleigh, NC 27695-8204

Abstract: A method for the conversion of a triol to a tetrahydrothiophene is described in which the key step involves ring cleavage of a cyclic carbonate with loss of carbon dioxide.

Breynolide is the aglycon hydrolysis product of Breynin A, a novel sulfur-containing glycoside that displays hypocholesterolemic activity in rats given daily oral doses in the μg/kg range. [1] The synthesis of (+)-breynolide has been described by Williams and co-workers [2a] and of racemic breynolide by Smith and co-workers. [2b] We envisioned that breynolide could be obtained from an acyclic mixed stannyl substituted acetal by an application of the electrophilic carbonyl ylide methodology we have recently developed. [3] Our synthetic strategy required the development of a method for the construction of the tetrahydrothiophene (THT) portion of the molecule from an unprotected triol. We now wish to report a novel route for the synthesis of THTs and the asymmetric synthesis of the THT portion of breynolide.

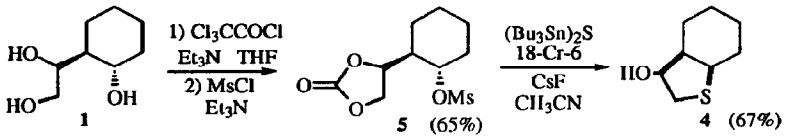
Cyclohexane triol **1** was prepared by copper catalyzed vinyl Grignard addition to cyclohexene oxide followed by oxidation of the vinyl group with osmium tetraoxide. Formation of the epoxy alcohol **2** was accomplished using 1 equivalent of mesyl chloride and triethylamine. Subsequent mesylation of the alcohol followed by reaction with Na_2S in DMF [2c] resulted in low yields of the THT product **4** (30-40%). As an alternative, we envisioned using a cyclic carbonate derivative of the 1,2-diol as the activating group for THT



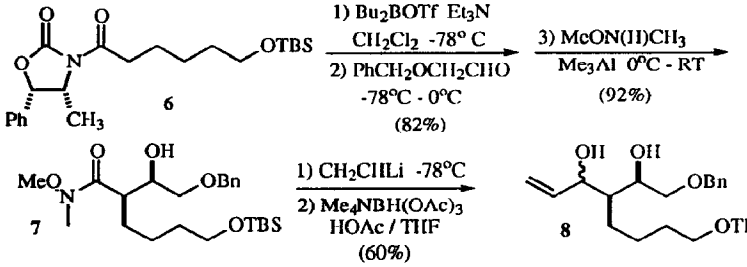
1 **2** (65%) **3** (93%) **4** (<40%)

formation. The carbonate could also potentially serve as a protecting group for alternate strategies in the late stages of the construction of breynolide whereas the epoxide could not. Reaction of triol **1** with carbonyl bisimidazole [4] did not provide the five membered cyclic carbonate cleanly. Improved regioselectivity was obtained by reaction of the triol with trichloroacetyl chloride. [5] Mesylation then provided the sulfonate/carbonate derived triol **5**. Reaction of **5** with Na_2S surprisingly led to good yields (>70%) of the cis fused tetrahydrofuran (THF) derivative rather than the THT. Presumably the hydroxide present in Na_2S undergoes competitive attack at either the carbonate carbonyl or the primary carbon of the cyclic carbonate followed by

intramolecular displacement of the mesylate by the primary alcohol. All attempts to reduce this undesired process when Na_2S was used as the source of sulfur were unsuccessful. We then examined Harpp's reagent, $(Bu_3Sn)_2S$, as an alternative source of S^{2-}. [6] Reaction of **5** with Harpp's reagent in the presence of 18-crown-6 and CsF did provide the THT **4** in reasonable yield without detectable amounts of competitive THF formation. Clearly the THF by-product noted above must arise from the presence of hydroxide. We were then able to turn our attention to the synthesis of the THT portion of breynolide using this protocol.

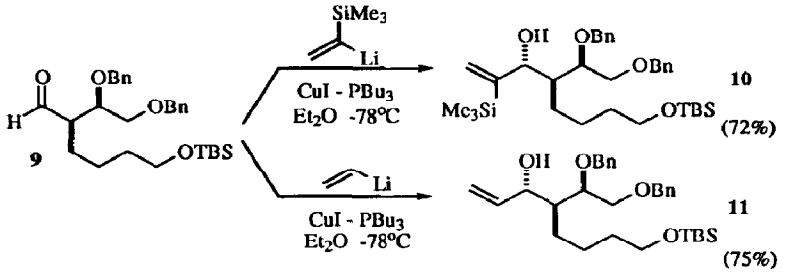


Asymmetric aldol reaction [7] of the oxazolidinone **6** and α-benzyloxyacetaldehyde gave the aldol product as a single diastereomer. [8] The purity of the aldehyde was critical to obtaining good results in the aldol reaction. Conversion to the Weinreb amide [7] **7** followed by addition of vinyllithium then gave the vinyl ketone in very good yield. Reduction of the β-hydroxy ketone using the procedure of Evans and co-workers [9] surprisingly resulted in only a 2-3:1 selectivity for the anti-1,3-diol **8**. Several trials were carried out for this reduction with modification of each reaction parameter without any improvement in stereoselectivity. It is interesting to note

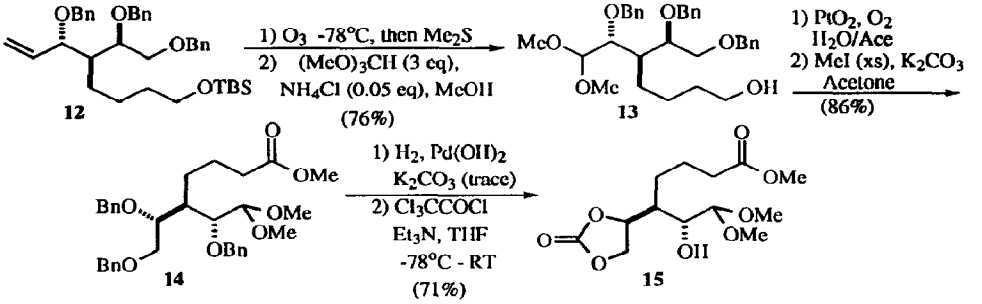


that a literature survey revealed that the synthesis of anti-1,3-diols by the reduction of aldol products does not appear to have been accomplished on unsaturated ketones, nor on systems which bear long aliphatic chains at the α-position. These structural features may impair formation of the cyclic transition state thereby leading to reduced stereoselectivity for the reduction. We then sought to improve the stereoselection for the anti-1,3-diol moiety by an alternative approach. Burke and co-workers [10] have demonstrated that stereoselective nucleophilic addition of a vinyl group to similar aldehydes was only accomplished by using tributyl phosphine stabilized cuprates derived from α-bromovinyltrimethylsilane. The addition reaction of an unsubstituted vinyl cuprate was not stereoselective. Benzylation of the amide **7** (NaH, BnBr, cat Bu4NI, 0°C - RT in DMF, 98%) followed by DIBAL reduction (THF, -78 °C, 2 h, 93%) provided the aldehyde **9** without any detectable racemization. Addition of the trimethylsilyl (TMS) substituted vinyl cuprate provided the alcohol **10** in good yield as a single diastereomer. Although the TMS substituent can be removed under a variety of conditions, [10] we also investigated the stereoselectivity of the addition of vinyl cuprate as a means to avoid the additional steps for TMS removal. We were gratified to observe that the addition reaction with the unsubstituted vinyl cuprate species also resulted in a single diastereomer of the desired anti-1,3-diol product **11**. Benzylation of the alcohol (as described above) then gave the tribenzyl/silyl ether **12**. Direct comparison of the derivatized vinyl addition

product could then be made with the same derivative obtained from the reduction of the β-hydroxy ketone.

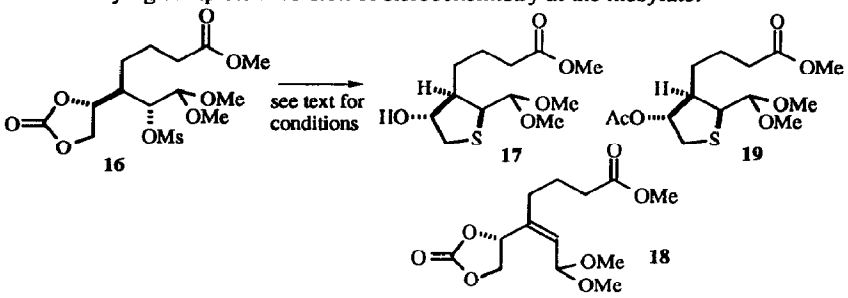


NMR and TLC data clearly revealed the absence of the syn-1,3-diol isomer. Ozonolysis of the vinyl group and conversion to the dimethyl acetal provided hydroxy acetal **13** by in-situ loss of the TBS group during acetalization. Oxidation of the primary alcohol to the acid was best carried out using PtO_2 [11] followed by esterification with MeI and potassium carbonate in acetone. PDC oxidation of the acetal intermediate **13** gave



lower yields; however, oxidation of the primary alcohol (TBAF removal of the TBS group, 99%) prior to ozonolysis of the vinyl group can be readily accomplished with PDC (overall yield of methyl ester, 77%). In either sequence, ozonolysis was carried out in the presence of Sudan III to prevent possible oxidation of the benzyl ethers. [12] Removal of the benzyl groups from **14** was then affected by hydrogenation in ethanol using $Pd(OH)_2$ as the catalyst. Optimal results were obtained if a trace of potassium carbonate was added to the reaction mixture. The triol was not chromatographed, but directly converted to the carbonate **15** in 71% overall yield. The structure of the five membered cyclic carbonate was confirmed by the ^{13}C NMR chemical shift for the carbonate carbonyl. [13] The mesylate **16** was then obtained in quantitative yield (MsCl, Et_3N, THF, -40°C, 1.5 h). Formation of the THT derivative proved to be solvent and temperature sensitive. Reaction of **16** with $(Bu_3Sn)_2S$ (0.6 eq), 18-Crown-6 (0.2 eq), and CsF (6.0 eq) in acetonitrile at 95°C resulted in a mixture of products. In addition to recovered starting material, THT **17** was obtained in only 13% yield along with 30% of an elimination product identified (NMR) as **18**. No indication of competing formation of a THF derivative was observed. Repeating the reaction in a mixture of ethyl acetate and DMF gave better results. Using $(Bu_3Sn)_2S$ (4.0 eq), 18-Crown-6 (1.0 eq), and CsF (40 eq) in 5:1 DMF:EtOAc at RT to 75°C (50 h) provided THT **17** in 60% yield along with 18% of the starting material. Only a trace of the alkene was observed. Carrying out the reaction with the same stoichiometry at temperatures up to 85°C for 66 h resulted in the formation of the THT (46%) and the unanticipated acetate **19** (24%). ^1H and ^{13}C NMR studies revealed that THT **17** was obtained

as a single isomer. The relative stereochemistry of the THT C2 substituent was determined by 2D NMR (DEPT, COSY) experiments verifying complete inversion of stereochemistry at the mesylate.



16 17 18 19

In summary, we have presented a novel approach to the synthesis of THTs by the ring cleavage of cyclic carbonates using Harpp's reagent. In addition, the asymmetric synthesis of THT **17** also revealed several unanticipated results in the stereoselective synthesis of anti-1,3-diols from β-hydroxy ketones. Application of **17** in the synthesis of breynolide will be reported in due course.

Acknowledgments Financial support from the National Institutes of Health (GM 47275) is gratefully acknowledged. NMR instrumentation at NCSU was made available by grants from the NC Biotechnology Center and the National Science Foundation (CHE-9121380). NSC thanks the Burroughs Wellcome Fund for fellowship support and the NCSU PLU chapter for a travel award.

References and Footnotes

1. Trost, W. *IRCS Med. Soc.* **1986**, *14*, 905.
2. (a) Williams, D. R.; Jass, P. A.; Tse, H-L. A.; Gaston, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4552-4554. (b) Smith, III, A. B.; Empfield, J. R.; Rivero, R. A.; Vaccaro, H. A.; Duan, J. J. W.; Sulikowski, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 9419-9434. See also, (c) Nishiyama, S.; Ikeda, Y.; Yoshida, S. I. *Tetrahedron Lett.* **1989**, *30*, 105-108. (d) Martin, S. F.; Daniel, D. *Tetrahedron Lett.* **1993**, *34*, 4281-4284. (e) Smith, III, A. B.; Gallagher, R. T.; Keenan, T. P.; Furst, G. T.; Dormer, P. G. *Tetrahedron Lett.* **1991**, *32*, 6847-6850.
3. (a) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438-7439. (b) Linderman, R. J.; Viviani, F. G.; Kwochka, W. R. *Tetrahedron Lett.* **1992**, *33*, 3571-3574.
4. Kutney, J. P.; Ratcliffe, A. H. *Syn. Commun.* **1976**, *5*, 47-52.
5. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699-1706.
6. (a) Harpp, D. N.; Gingras, M. *Tetrahedron Lett.* **1987**, *28*, 4373-4376. (b) Gingras, M.; Chan, T. H.; Harpp, D. N. *J. Org. Chem.* **1990**, *55*, 2078-2090. (c) Harpp, D. N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, *110*, 7737-7745. (d) Harpp. D. N.; Gingras, M.; Aida, T.; Chan, T. H. *Synthesis* **1987**, 1122-1124.
7. See, Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031, for experimental procedures used for the aldol reaction with this aldehyde.
8. All new compounds were fully characterized by spectral data and MS or combustion analysis.
9. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.
10. Burke, S. D.; Piscopio, A. D.; Marron, B. E.; Matulenko, M. A.; Pan, G. *Tetrahedron Lett.* **1991**, *32*, 857-858.
11. Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899-3902. Ultrasound (ultrasonic cleaner bath) was used to promote the oxidation, see: Majetich, G.; Song, J. S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030-1037.
12. Veysoglu, T.; Mitschler, L. A.; Swayze, J. K. *Synthesis* **1980**, 807-810.
13. ^{13}C NMR of the cyclic carbonate CO was observed at 154.9 ppm; IR 1780 cm^{-1}.

(*Received in USA* 17 *June* 1994; *accepted* 22 *July* 1994)