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A Chiral Pool Approach to the Synthesis of Optically Active Tetrahalo Norbornyl Building Blocks

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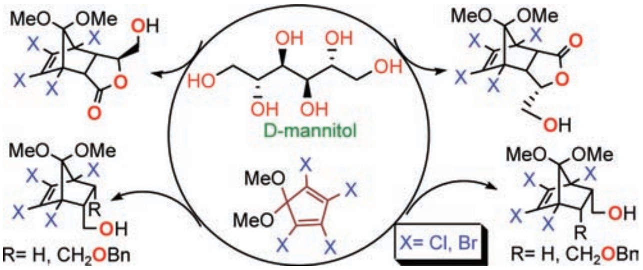
ABSTRACT



Optical antipodes of the mono- and disubstituted polyhalo norbornyl derivatives were prepared in excellent yields. The monosubstituted derivatives 7 were obtained with good enantiopurities. A kaleidoscopic change in the product formation and distribution was observed by changing the chronology of reactions.

Chiral pool synthesis is one of the main approaches to enantiopure organic compounds apart from asymmetric synthesis and resolution of racemates. It involves the synthesis of complex optically active compounds from a stockpile of easily available enantiomerically pure compounds. The built-in chirality present in the starting material is then preserved or creatively used to generate more chiral centers employing chosen methods in the run of reactions toward the target molecule.[1] Despite the presence of various other methods to reach the optically active targets, the chiral pool approach has carved a niche for itself and is widely employed wherever it is viable. Unlike other resources, the chiral pool is renewable and devoid of any strategic holdings.[2]

The tetrahalonorbornyl derivatives which are readily accessible via a Diels−Alder reaction between diene **1a** or**1b** and a suitable dienophile have served as illustrious rigid templates in organic synthesis. The importance can be attributed to the high degree of regio- and stereocontrol, which are exploited in the synthesis of complex multistereo natural products, intermediates, and aesthetically pleasing novel molecular entities.[3] However, most of the applications known with the tetrahalodimethoxy norbornyl derivatives were with the racemic compounds.[3] In the few reports known, the optically active compounds were obtained by kinetic resolution.[4] Our interest in norbornyl derivatives as building blocks in organic synthesis[5] prompted us to check for the reactions of **1a**,**b** with dienophiles obtained from renewable sources.

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(1) (a) Hanessian, S. *Total Synthesis of Natural Products: The ‘Chiron’ Approach*; Baldwin, J. E., Ed.; Pergamon: Oxford, UK, 1983. (b) Nugent, W. A.; Rajanbabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479.

(2) Taylor, M. S.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5368.

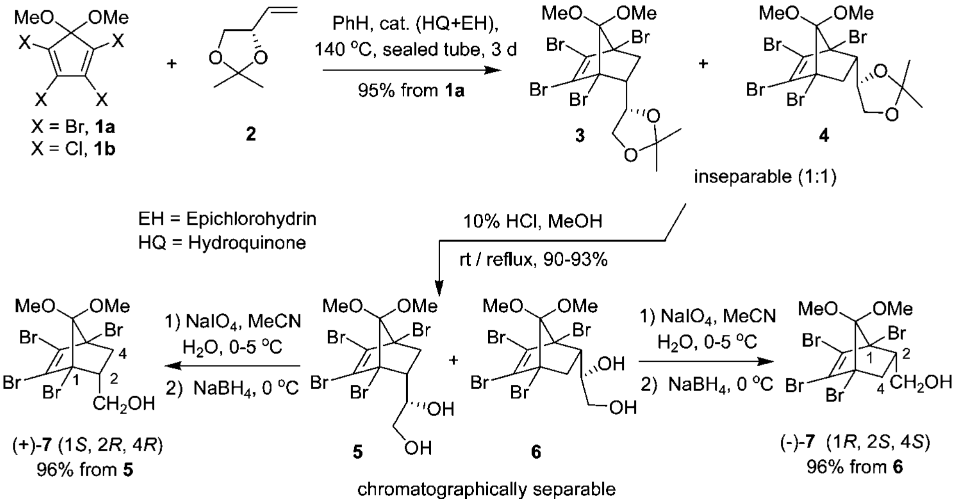
(3) Khan, F. A.; Das, B. P.; Dash, J. *J. Prakt. Chem.* **2000**, *342*, 512, and references therein.

(4) (a) de Oliveira, L. F.; Costa, V. E. U. *Tetrahedron Lett.* **2006**, *47*, 3565. (b) Berger, B.; Rabiller, C. G.; Konigsberger, K.; Faber, K.; Griengl, H. *Tetrahedron: Asymmetry* **1990**, *1*, 541, and references therein.

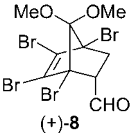
(5) For selected list of reports on the applications of norbornyl derivatives from our group, see: (a) Khan, F. A.; Rout, B. *J. Org. Chem.* **2007**, *72*, 7011. (b) Khan, F. A.; Rout, B. *Tetrahedron Lett.* **2006**, *47*, 5251. (c) Khan, F. A.; Rao, C. N. *Tetrahedron Lett.* **2006**, *47*, 7567. (d) Khan, F. A.; Dash, J.; Sudheer, Ch.; Sahu, N.; Parasuraman, K. *J. Org. Chem.* **2005**, *70*, 7565. (e) Khan, F. A.; Dash, J. *Eur. J. Org. Chem.* **2004**, 2692. (f) Khan, F. A.; Dash, J.; Sudheer, Ch. *Chem. Eur. J.* **2004**, *10*, 2507. (g) Khan, F. A.; Satapathy, R.; Dash, J.; Savitha, G. *J. Org. Chem.* **2004**, *69*, 5295. (h) Khan, F. A.; Dash, J.; Sahu, N.; Sudheer, Ch. *J. Org. Chem.* **2002**, *67*, 3783. (i) Khan, F. A.; Sahu, N.; Dash, J.; Prabhudas, B. *J. Indian Inst. Sci.* **2001**, *81*, 325.

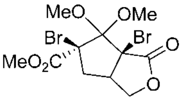
10.1021/ol800990m CCC: $40.75

Scheme 1



Dienophile **2**, which is easily accessible from d-mannitol[6] was heated along with a benzene solution of the diene **1a** in a sealed tube to afford the inseparable diastereomers **3** and **4** in excellent yield (95%, Scheme 1). A catalytic amount of hydroquinone plays the role of a radical scavenger while epichlorohydrin helps in quenching any acidic impurities that might be generated during the reaction. The diastereomeric ratio (1:1) was determined from the ^{1}H NMR analysis. Removal of acetonide protection under acidic conditions afforded the diastereomeric mixture of diols **5** and **6**, which were separated by column chromatography.

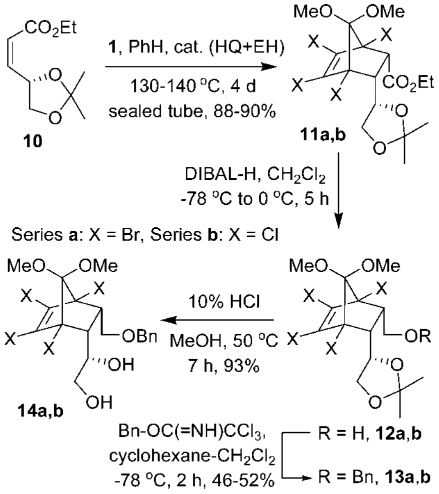

(+)-**8**


(-)-**9**

Optically active tetrabromo adduct (+)-**7** was obtained in excellent yield by cleavage of diol **5** followed by reduction of the resulting aldehyde (+)-**8**. The enantiomeric purity of the alcohol (+)-**7** was found to be >99%, which is much higher than that reported in the literature.[7] The aldehydes (+)- and (−)-**8**, precursors for optical antipodes (+) and (−)-**7**, are very useful compounds. The racemic aldehyde **8** was utilized by us in the recent past for the synthesis of racemic *trans*-hydrindan derivatives.[5g] The enantiopure aldehydes **8** were used for the synthesis of tetracyclic amines.[8] Further, (−)-**7** was converted to γ-lactone fused cyclopentanoid (−)-**9** following a protocol that was reported by us earlier.[5h] γ-Lactone-fused cyclopentanoids are important substructures found in umpteen number of natural products and are important intermediates in organic synthesis.[9] The present method provides a simple route to the synthesis of one such optically active intermediate.

After successfully preparing the monosubstituted norbornyls **7**, we turned our attention to the synthesis of optically pure disubstituted polyhalo norbornyl derivatives. For this purpose, we envisaged that **10** would be a good choice as dienophile.[10] Engrossed by the number of theoretically possible products that can be obtained, we carried out the Diels−Alder reaction of **1a**,**b** with **10**. Interestingly, out of the two possible *endo* isomers, only **11** was formed in excellent yields (Scheme 2).

Scheme 2



While the possibility of *exo*-adduct formation is ruled out because of the intrinsic *endo* selectivity of the dienes **1a**,**b**,

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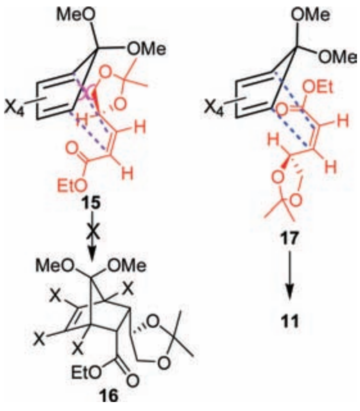
(6) (a) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852.

(7) Mamedov, E. G. *Russ. J. Org. Chem.* **2002**, *38*, 15. In this report, the Diels−Alder adduct of **1a** and (−)-menthyl acrylate was transformed to **7** without specifying if a single diastereomer was formed. Even the authentic **7** obtained by repeated crystallization of acrylic acid adduct with (−)-ephedrine, assumed to be optically pure, appears to have an ee of 66%. We came to this conclusion by comparing the specific rotation values obtained by us and Mamedov. We confirmed the enantiopurity of **7** obtained by our method using chiral HPLC.

(8) Khan, F. A.; Upadhyaya, S. K. Unpublished results.

the transition states **15** and **17** provide a plausible explanation for the formation of single *endo*-diastereomer. We presume that the allylic 1,3-strain causes the dienophile to orient in a way so as to accommodate the smallest group on the allylic chiral center, present in the molecular plane, in the cavity as depicted in Scheme 3.[11] The TS **15** leading to **16** is disfavored due to steric crowding, while TS **17** devoid of such problem leads to products **11**.

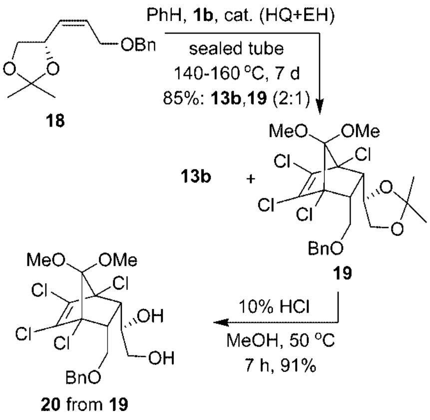
Scheme 3



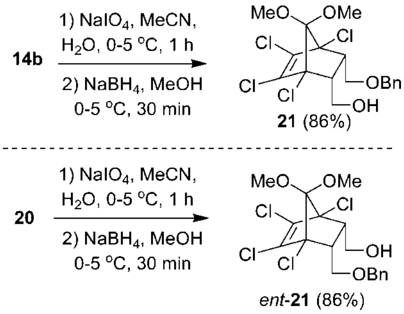
DIBAL-H reduction of **11a**,**b** resulted in the alcohols **12a**,**b**. Attempted benzylation of the free hydroxyl in **12a**,**b** with benzyl halides employing various bases (NaH, *n*-BuLi, etc.) or Ag$_2$O condition afforded a complex reaction mixture. None of the components resulted were benzyl derivatives as noted from ^{1}H NMR spectra. However, benzylation could be effected with benzyl trichloroacetimidate albeit with modest yields. Another problem here was with the purification of benzyl ethers from the trichloroacetamide impurities generated. Acetonide deprotection of **13a**,**b** under acidic conditions yielded the diols **14a**,**b**.

To circumvent the problems associated with benzylation of **12a**,**b**, the chronology of reactions was changed. As per the strategy, the benzyl protection was installed at the dienophile stage and then the Diels–Alder reaction was carried out with the diene **1b**. DIBAL-H reduction of **10** followed by benzyl protection of the resulting alcohol with *n*-BuLi and BnBr afforded the benzyl ether **18** in excellent yield.[12] Diels–Alder reaction of the dienophile **18** with diene **1b** yielded an isomeric mixture of products (Scheme 4). Although a mixture of diastereomers is obtained, the selectivity was in favor of the diastereomer formed via alternate route (**13b** in Scheme 2). The minor diastereomer **19** was subjected to acetonide deprotection under acidic condition to give diol **20** in 93% yield. The diastereomeric diols **14b** and **20** were separately subjected to NaIO$_4$ cleavage followed by NaBH$_4$ reduction resulting in the formation of antipodal monoprotected diol derivatives **21** and *ent*-**21** (Scheme 5).

Scheme 4



Scheme 5



Treating **11b** with 10% HCl in MeOH afforded a mixture of lactones **22** and **23** (Scheme 6). While the formation of lactones was confirmed from NMR and IR spectra, it was not possible to distinguish the two isomers with certainty. With the intent of reconfirming the stereochemistry of the lactone **22**, we have carried out Diels–Alder reaction of the cyclic dienophile **24**[13] with the dienes **1a**,**b**. These reactions resulted in intractable reaction mixtures, possibly due to the presence of free hydroxyl group in **24**. To circumvent this problem, the hydroxyl was protected as TBS ether **25** which was then subjected to Diels–Alder reactions with **1a**,**b**. Removal of TBS protection from the resulting compounds gave the lactones **26a**,**b**. The lactone **26b** was found to be different from that obtained by the hydrolysis of **11b**. The formation of the lactones **26a**,**b** can be explained from the

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(9) For selected examples, see references cited in ref 5h.

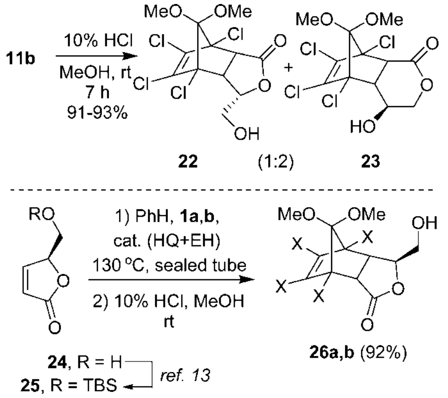
(10) (a) Haefele, B; Jäger, V. *Liebigs Ann. Chem.* **1987**, 85. For a reaction of dienophile **10** with cyclopentadiene, see: (b) Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Tetrahedron Lett.* **1985**, *26*, 1631. (c) Casas, R.; Parella, T.; Branchadell, V.; Oliva, A.; Ortuñ o, R. M.; Guingant, A. *Tetrahedron* **1992**, *48*, 2659.

(11) A distorted Felkin–Anh TS was invoked by Mulzer[10b] to explain the observed diastereoselectivity for the reaction of **10** with cyclopentadiene which furnished a mixture of *endo*/*exo* (85:15) isomers while Ortuño, who obtained a mixture of *endo*/*exo*/*endo* (78:15:7) isomers for the same reaction,[10c] proposed steric and electronic factors play a crucial role.

(12) (a) Sugisaki, C. H.; Ruland, Y.; Le Clezio, I.; Baltas, M. *Synlett* **2001**, 1905. (b) Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391.

(13) Mann, J.; Weymouth-Wilson, A. C. *Org. Synth.* **1998**, *75*, 139.

Scheme 6



transition states involved. Further, a report by Ortuño and Font[14] which describes the Diels−Alder reaction of cyclopentadiene with **24** substantiates the formation of **26a**,**b**.

Finally, to rule out any ambiguity, single-crystal X-ray analysis of the chloro derivatives **22** and **23** was carried out. These studies have established that the minor isomer is γ-lactone (**22**) and the major isomer is δ-lactone (**23**). From this, the absolute configurations of **11a**,**b** can be established, which will eventually dodge out the uncertainties of absolute configurations of all the compounds described here.

In conclusion, we have described efficient syntheses of various optically active tetrahalo norbornyl derivatives from abundantly available, cheap starting materials d-mannitol and cyclopentadiene.[15] The Diels−Alder reactions with the 1,2-disubsituted optically active dienophiles are highly stereoselective and interesting changes in the product formation and distribution were observed upon changing the chronology of the reactions.

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Note Added after ASAP Publication. Due to a production error structures **8** and **9** were added to the version published June 17, 2008.

Supporting Information Available: Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C spectra, and details on the X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Ortuño, R. M.; Corbera, J.; Font, J. *Tetrahedron Lett.* **1986**, *27*, 1081.

[15] Dienes **1a**,**b** and and dienophiles **2**, **10**, **18**, and **25** are prepared from cyclopentadiene and d-mannitol, respectively.