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Enantioselective Construction of Carbobicyclic Scaffolds

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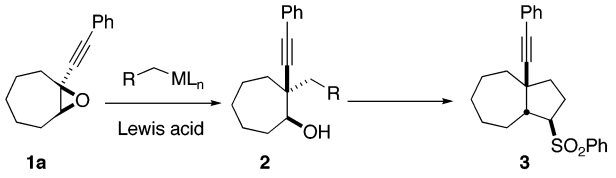
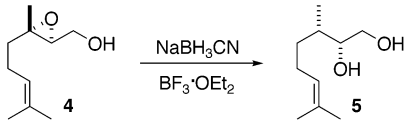
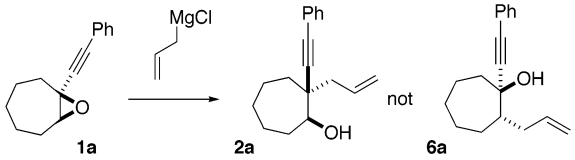
Carbocycles, as exemplified by morphine and the steroids, can be potent drugs. Although computationally based receptor binding analysis can lead to potential new drug candidates that are polycarbocyclic, such leads are often not pursued, because of the perception that even if it turned out to be active, an enantiomerically pure polycarbocyclic agent would be too expensive to manufacture. We report a simple, efficient route to enantiomerically pure carbobicyclic scaffolds such as **3** starting from prochiral cyclic ketones.[1]



Bicyclic epoxides such as **1a**[1] were available in high enantiomeric purity using the method of Shi.[2] The key to our proposed approach was the selective opening of **1a** at the more substituted carbon atom with an sp^3-hybridized organometallic nucleophile[3] to give **2**. We envisioned that if the right combination of Lewis acid, to activate the epoxide, and nucleophilic organometallic could be found, such a selective opening might be possible. A precedent for this approach was the addition of hydride to geraniol epoxide **4**.[4]

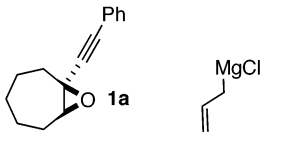
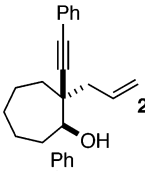
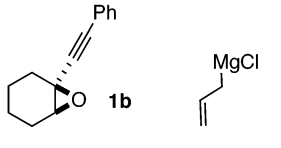
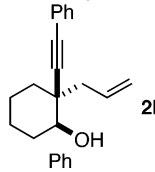
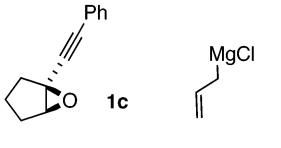
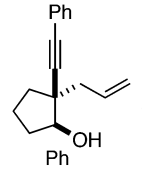
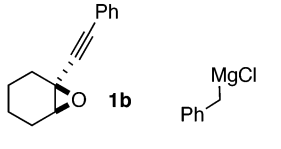
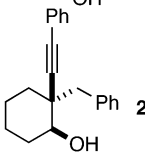
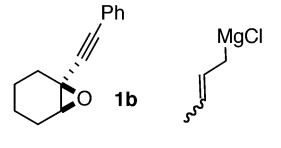
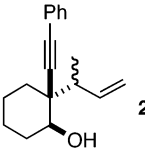
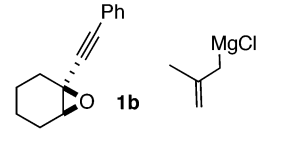
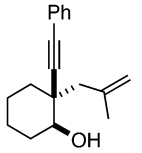


The challenge of opening epoxide **1a** at the more substituted carbon atom turned out to be much easier than we had anticipated. We were pleased to observe that uncatalyzed allylmagnesium chloride[5] smoothly opened **1a** to give the secondary alcohol **2a**. X-ray analysis of the derived 3,5-dinitrobenzoate confirmed that the opening had proceeded with inversion of configuration.



Five- and six-membered ring epoxides (Table 1) gave similar results. We expect that the opening of the oxirane proceeds through a "borderline S_N2" mechanism,[6] with the alkyne stabilizing the incipient positive charge. We briefly explored alternative nucleophiles with the epoxide **1b**. We found that allylic and benzylic Grignard reagents gave the desired ring-opening products (entries 4−6 in Table 1). This promises to be a general method for the direct enantioselective construction of quaternary centers that are part of carbocyclic rings.[7]

Table 1. Opening of Bicyclic Epoxides with Grignard Reagents[a]

Entry	Starting material	Grignard	Product(s)	Yield (%)
1	 **1a**		 **2a**	83
2	 **1b**		 **2b**	88
3	 **1c**		 **2c**	88
4	 **1b**		 **2d**	84
5	 **1b**		 **2e**[b]	85[c]
6	 **1b**		 **2f**	76

[a] Typical procedure for opening of epoxides: Grignard reagent (4−5 equiv) was added under N_2 into a THF solution of epoxide at 0 °C. The resulting solution was warmed slowly to room temperature and stirred at this temperature overnight. [b] Two isomers are in a 2:1 ratio, which was determined by ^1H NMR. [c] Combined yield of two isomers.

While the enantioselectivity of cyclopentene and cyclohexene epoxidation by the Shi protocol had been reported,[2] the enantioselectivity of cycloheptene epoxidation was not known. We determined that **2a** was a 13.6:1 mixture of enantiomers.[8] The absolute configuration of **2a** was confirmed by conversion (Scheme 1) to the ketone **8**, $[\alpha]_D = -36.3$ (*c* 0.9, THF, ee = 86%), lit[9] $[\alpha]_D = -20.7$ (*c* 2.8, THF, ee = 51%).

The epoxidation and ring opening sets two stereogenic centers. We found that, as we had anticipated, intramolecular alkylation proceeded smoothly to establish cis carbobicyclic ring systems (Table 2). The results in Table 2 demonstrate that a variety of cis carbobicyclic scaffolds can be constructed. The alkynyl and sulfonyl

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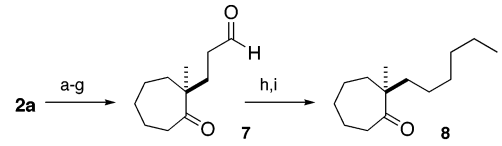
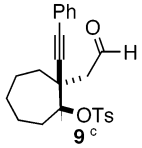
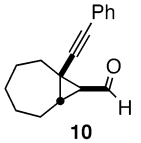
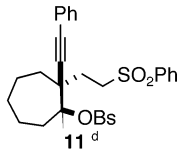
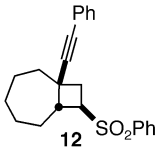
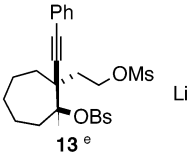
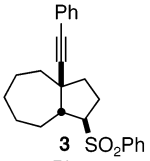
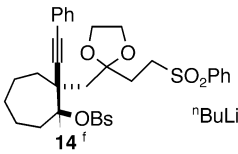
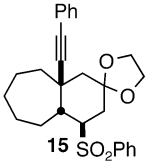
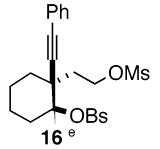
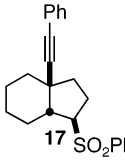
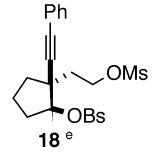
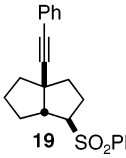
Scheme 1[a]



[a] Reagents and conditions: (a) 9-BBN, THF; NaOH, H_2O_2 (ref 10); (b) Pd/$BaSO_4$, pyridine, H_2; (c) NaH, TBAI, THF, BnBr, reflux; (d) O_3, CH_2Cl_2; PPh_3; (e) N_2H_4, $HOCH_2CH_2OH$, 210 °C; (f) H_2, Pd/C, EtOH; (g) Dess−Martin reagent (ref 11), CH_2Cl_2; (h) $^nPr^+PPh_3Br^-$, ^{t}BuOK, THF; (i) H_2, Pd/C, EtOH.

Table 2. Construction of Cis Carbobicyclic Ring Systems

Entry	Starting materials	Reagent	Product [a, b]	Yield (%)
1	 **9** [c]	^{t}BuOK	 **10**	88
2	 **11** [d]	^{n}BuLi	 **12**	83
3	 **13** [e]	$LiCH_2SO_2Ph$; ^{n}BuLi	 **3**	72
4	 **14** [f]	^{n}BuLi	 **15**	92
5	 **16** [e]	$LiCH_2SO_2Ph$; ^{n}BuLi	 **17**	85
6	 **18** [e]	$LiCH_2SO_2Ph$; ^{n}BuLi	 **19**	86

[a] All products are single diastereomers. [b] Ref 12. [c] Starting from **2a**, TsCl, pyridine, DMAP; O_3, CH_2Cl_2; PPh_3. [d] Starting from **13**, NaOH, PhSH; mCPBA. [e] Starting from **2a**, **2b**, and **2c**, BsCl, pyridine, DMAP; O_3, CH_2Cl_2, MeOH; $NaBH_4$; MsCl, Et_3N, CH_2Cl_2. [f] Starting from **2a**, BsCl, pyridine, DMAP; mCPBA, CH_2Cl_2; $BF_3{\cdot}Et_2O$, $LiCH_2SO_2Ph$ (ref 13); Dess−Martin reagent, CH_2Cl_2; $HOCH_2CH_2OH$, THF, $HC(OEt)_3$ (ref 14).

groups are versatile and can be converted into other functional groups. It is also possible to include other functional groups in the ring, as shown in entry 4.

While many methods for polycarbocyclic ring construction have been developed, only a few of these lead directly to enantiomerically pure products. We expect that the approach to enantiomerically pure carbobicyclic scaffolds outlined here will be of general utility in the stereocontrolled construction both of natural products and of drug candidates.

Acknowledgment. We thank the NIH (GM60287) for financial support of this work, James A. Golen for the X-ray analysis, and John Dykins for the high-resolution mass spectra. This work is dedicated to the memory of David L. Coffen, a master of the science of asymmetric synthesis.

Supporting Information Available: Experimental details and spectra for all new compounds (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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