Enantioselective Synthesis of "Quaternary" 1,4-Benzodiazepin-2-one Scaffolds via Memory of Chirality

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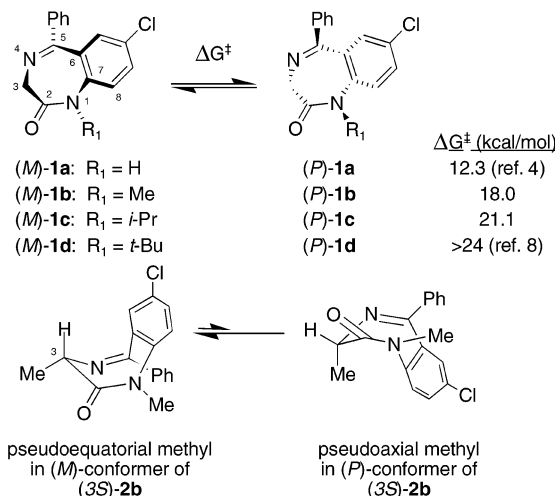Received June 9, 2003; E-mail: pcarlier@vt.edu

1,4-Benzodiazepines are among the most important scaffolds in medicinal chemistry, representing the prototypical "privileged structure".[1] Tens of thousands of these compounds have been prepared on solid phase and in solution, and the development of new 1,4-benzodiazepine drug candidates shows no sign of abating.[2] Yet amidst this impressive diversity, the reliance of most of these syntheses upon proteinogenic amino acid starting materials has systematically excluded one class of targets: enantiopure benzodiazepines possessing a quaternary stereogenic center.[3] In this Communication, we report an enantioselective α-alkylation route to "quaternary" 1,4-benzodiazepin-2-ones that relies upon the intrinsic chirality of the benzodiazepine ring.

Despite the absence of a stereogenic center, glycine-derived 1,4-benzodiazepin-2-ones **1** such as diazepam (**1b**) are chiral,[4,5] existing as (*M*)- and (*P*)-conformational enantiomers[6] (Scheme 1). When the N1 substituent is relatively small (H, Me, *i*-Pr, i.e., **1a**−**c**), racemization is facile at room temperature, preventing resolution of these compounds.[4,7] Only when the N1 substituent is very large (e.g., **1d**, R₁ = *t*-Bu) is the racemization barrier high enough to allow preparative resolution of the (*M*)- and (*P*)-enantiomers.[4,8]

It is well known[5,8−10] that placement of a single substituent at C3 perturbs the conformational equilibrium of *N*-Me 1,4-benzodiazepin-2-ones (e.g., **2b**), stabilizing the pseudoequatorial conformer; thus, (3*S*)-stereochemistry will induce the diazepine ring to adopt the (*M*)-conformation (Scheme 1). We envisioned that the effective stereochemical cooperativity demonstrated by 3-alkyl-1,4-benzodiazepin-2-ones such as **2b** might allow the development of an enantioselective α-alkylation protocol. Although deprotonation of (3*S*)-**2b** would destroy the stereogenic center at C3, the resulting enolate would remain chiral by virtue of the nonplanar diazepine ring. Deprotonation/alkylation sequences of glycine-derived 1,4-benzodiazepin-2-ones have been previously reported[11] as a means to prepare novel benzodiazepines and the corresponding amino acids, including an auxiliary-based asymmetric method.[11b] However, the only reported α-alkyation route to 3,3-dialkyl-1,4-benzodiazepin-2-ones affords low (0−20%) yields.[11a]

Enantiomerically pure 1,4-benzodiazepin-2-ones (3*S*)-**2a** and (3*S*)-**3a** (R₁ = H) were prepared in 91% and 67% yield from (*S*)-Boc-Ala and (*S*)-Boc-Phe, using a modification of Shea's protocol.[12] Conversion to the *N*-Me (**2b** 94%) and the *N*-*i*-Pr derivatives (**2c** 82%; **3c**, 58%) in 100% ee was achieved upon treatment of the sodium salts with the corresponding alkyl triflates.[13] After considerable optimization, we determined that acceptable yields of desired α-alkylation products could be attained by deprotonating **2b**−**c** and **3c** with LDA in the presence of HMPA, and treatment with *n*-BuLi before addition of the electrophile (Table 1).[14] However, application of this protocol to the enolate of *N*-Me benzodiazepine (3*S*)-**2b** and BnBr gave **4** in a disappointing 0% ee. Fortunately, identical treatment of the *N*-*i*-Pr analogue (3*S*)-**2c** gave the desired product **5** in 97% ee (Table 1, cf. entries 1, 2). Knowing that the inversion barrier of benzodiazepines is a function of the size of the N1 substituent (Scheme 1), we reason that an *N*-Me group is not large enough to impart sufficient conformational stability to the enolate ring at −78 °C on the deprotonation/alkylation time scale. Even with short deprotonation times (LDA only, 10 s), *N*-Me benzodiazepine (3*S*)-**2b** produces racemic **4**. In contrast, deprotonation/trapping reactions of the *N*-*i*-Pr analogues examined thus far are highly enantioselective. In addition to benzylation, reaction of the enolate derived from (3*S*)-**2c** with other active electrophiles proceeds

Scheme 1. Dynamic Chirality of **1a**−**c** and Stereochemical Cooperativity in **2b** (ΔG‡ Values Were Determined by ¹H NMR Spectroscopy (Coalescense))

	ΔG‡ (kcal/mol)
(*M*)-**1a**: R₁ = H ⇌ (*P*)-**1a**	12.3 (ref. 4)
(*M*)-**1b**: R₁ = Me ⇌ (*P*)-**1b**	18.0
(*M*)-**1c**: R₁ = *i*-Pr ⇌ (*P*)-**1c**	21.1
(*M*)-**1d**: R₁ = *t*-Bu ⇌ (*P*)-**1d**	>24 (ref. 8)

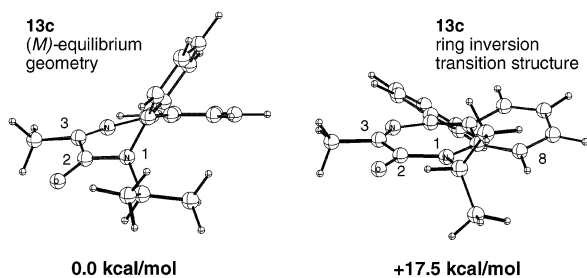pseudoequatorial methyl in (*M*)-conformer of (3*S*)-**2b**   ⇌   pseudoaxial methyl in (*P*)-conformer of (3*S*)-**2b**

Table 1. Racemizing (**2b**) and Enantioselective (**2c**, **3c**) Deprotonation/Trapping Reactions of 1,4-Benzodiazepin-2-ones

1. 1.2 equiv. LDA, 6 equiv. HMPA, THF, -78°C, 15 min; 1.2 equiv. n-BuLi, 15 min;
2. 10 equiv. E-X, -78 °C 0.5 to 10 hours
3. NH₄Cl (aq.)

4 - 10

	R₁	R₂
(3*S*)-(+)-**2b**	Me	Me
(3*S*)-(+)-**2c**	*i*-Pr	Me
(3*S*)-(+)-**3c**	*i*-Pr	Bn

| entry	R₁	R₂	Eᵃ	product	% yield	% eeᵇ
1	Me	Me	Bn	(±)-**4**	72	0ᶜ
2	*i*-Pr	Me	Bn	(+)-**5**	74	97 (3*R*)
3	*i*-Pr	Me	4-MeC₆H₄CH₂	(+)-**6**	68	95 (3*R*)
4	*i*-Pr	Me	2-PhC₆H₄CH₂	(+)-**7**	70	99
5	*i*-Pr	Me	allyl	(+)-**8**	76	94
6	*i*-Pr	Me	D	(+)-**9**	85ᵈ	99 (3*S*)
7	*i*-Pr	Bn	Me	(−)-**5**	64	95 (3*S*)
8	*i*-Pr	Bn	allyl	(+)-**10**	57	86

ᵃ Electrophiles used: BnBr, 4-MeC₆H₄CH₂Br, 2-PhC₆H₄CH₂Br, allyl bromide, D-OTFA, MeI. ᵇ % ee measured by chiral stationary phase HPLC (Chiralcel OD, AD). ᶜ Racemic **4** is also obtained if BnBr is added only 10 s after deprotonation by LDA. ᵈ The extent of deuteration is 96%.

Figure 1. B3LYP/6-31G* equilibrium geometry and ring inversion transition structure of *N-i*-Pr enolate anion **13c** (relative free energies at B3LYP/6-31+G*//B3LYP/6-31G*).

Scheme 2. Correlation of Benzodiazepines **5** and **6** by Conversion to the Corresponding Quaternary Amino Acids **11** and **12**
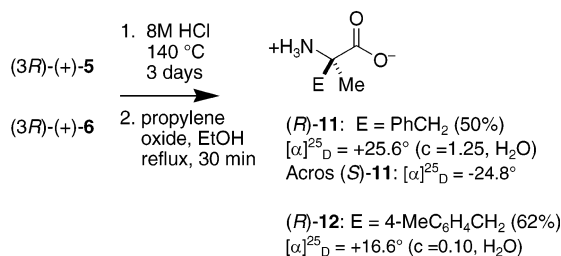
in 94−99% ee (Table 1, entries 3−6). High enantioselectivities are also observed in methylation and allylation of the enolate of Phe-derived (3*S*)-**3c** (Table 1, entries 7, 8). Interestingly, ¹H and ¹³C NMR spectroscopy demonstrate that, unlike **2c** and **3c**, 3,3-disubstituted benzodiazepines **4−8**, **10** exist as ∼1:1 mixtures of (*M*)- and (*P*)-conformers, consistent with the similar local steric demands of the C3 substituents.[15]

The stereochemical course of these reactions appears to be uniformly retentive. Retentive deuteration of the enolate of (3*S*)-(+)-**2c** was established by comparison of (+)-**9** with the starting material. Retentive alkylation of the enolate of (3*S*)-**2c** was established by hydrolysis of (+)-**5** and (+)-**6** to the corresponding quaternary amino acids **11** and **12** (Scheme 2).

Retentive conversion of Phe-derived (3*S*)-**3c** to (3*S*)-(−)-**5** was confirmed by HPLC and optical rotation (Table 1, entries 2, 7).

The transformations of **2c** and **3c** described above can be viewed as examples of Seebach's "self-regeneration of stereocenters (SRS)" principle.[16] The novel feature here is the use of dynamic, conformational chirality (rather than static, central chirality) to control alkylation stereochemistry of the enolates; from this perspective, these transformations also rely upon "memory of chirality".[17]

Dynamic chirality of the enolates is suggested by the sensitivity of the α-alkylation % ee to the size of the N1 substituent, and by the calculated (B3LYP/6-31G*) equilibrium geometries and ring inversion transition structures of the (des-chloro) enolate anions **13b,c** (derived from **2b,c**; **13c** depicted in Figure 1).[18] The equilibrium geometries of enolates **13b,c** are chiral and feature essentially flat C3 carbons (sum of angles 358.5°, 359.0°). The ring inversion transition structures of **13b,c** indicate near eclipsing of the N1 substituent (R_1) and C8 (dihedral angles 13.4°, 12.8°). B3LYP/6-31+G*//B3LYP/6-31G* activation free energies for ring inversion at 195 K of **13b** (*N*-Me) and **13c** (*N-i*-Pr) are 12.4 and 17.5 kcal/mol, which correspond to racemization $t_{1/2}$ (195 K) values of 0.11 min and 970 h, respectively. Thus, the divergent stereochemical outcomes for deprotonation/benzylation of **2b** and **2c**

(Table 1, entries 1, 2) may be rationalized. Finally, consistent with this high racemization $t_{1/2}$ estimate for **13c**, we find that, after a deprotonation time of 8 h at −78 °C, benzylation of the enolate of (3*S*)-**2c** occurs in 92% ee (cf. Table 1, entry 2).

Supporting Information Available: Experimental procedures, spectroscopic data and HPLC chromatograms, and computational details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirschfield, J. *J. Med. Chem.* **1988**, *31*, 2235−2246.
(2) (a) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132−143. (b) Wu, Z.; Ercole, F.; FitzGerald, M.; Perera, S.; Riley, P.; Campbell, R.; Pham, Y.; Rea, P.; Sandanayake, S.; Mathieu, M. N.; Bray, A. M.; Ede, N. J. *J. Comb. Chem.* **2003**, *5*, 166−171.
(3) The only published route to such compounds involves lipase-catalyzed acylation of prochiral 3,3-bis(hydroxymethyl)-1,4-benzodiazepin-2-ones: Avdagic, A.; Lesac, A.; Majer, Z.; Hollosi, M.; Sunjic, V. *Helv. Chim. Acta* **1998**, *81*, 1567−1582.
(4) Linscheid, P.; Lehn, J.-M. *Bull. Chim. Soc. Fr.* **1967**, 992−997.
(5) Konowal, A.; Snatzke, G.; Alebic-Kolbah, T.; Kajfez, F.; Rendic, S.; Sunjic, V. *Biochem. Pharm.* **1979**, *28*, 3109−3113.
(6) The sense of chirality of the ring has traditionally been described using the helical descriptors (*M*)- and (*P*)-, based on the sign of the τ_{2345} torsional angle. The same sense of chirality is noted using the more easily perceived $\tau_{(R1)178}$ or τ_{2176} torsional angles.
(7) Application of the Eyring equation allows the racemization $t_{1/2}$ values (298 K) of **1a−c** to be estimated as 60 μs, 0.9 s, and 2.8 min.
(8) Gilman, N. W.; Rosen, P.; Earley, J. V.; Cook, C.; Todaro, L. J. *J. Am. Chem. Soc.* **1990**, *112*, 3969−3978.
(9) Sunjic, V.; Lisini, A.; Sega, A.; Kovac, T.; Kajfez, F.; Ruscic, B. *J. Heterocycl. Chem.* **1979**, *16*, 757−761.
(10) Paizs, B.; Simonyi, M. *Chirality* **1999**, *11*, 651−658.
(11) (a) Reitter, B. E.; Sachdeva, Y. P.; Wolfe, J. F. *J. Org. Chem.* **1981**, *46*, 3945−3949. (b) Decorte, E.; Toso, R.; Sega, A.; Sunjic, V.; Ruzic-Toros, Z.; Kojic-Prodic, B.; Bresciani-Pahor, N.; Nardin, G.; Randaccio, L. *Helv. Chim. Acta* **1981**, *64*, 1145−1149. (c) Kim, K.; Volkman, S. K.; Ellman, J. A. *J. Braz. Chem. Soc.* **1998**, *9*, 375−379. (d) Goumri-Magnet, S.; Guerret, O.; Gornitzka, H.; Cazaux, J. B.; Bigg, D.; Palacios, F.; Bertrand, G. *J. Org. Chem.* **1999**, *64*, 3741−3744.
(12) Hart, B. R.; Rush, D. J.; Shea, K. J. *J. Am. Chem. Soc.* **2000**, *122*, 460−465.
(13) Less reactive alkylating agents (MeI, *i*-PrOTs) give partial racemization.
(14) No alkylation products are obtained in the absence of HMPA. If treatment of the enolate with *n*-BuLi is not carried out before trapping, alkylation and deuteration yields decrease, and significant amounts of starting material are recovered. We suspect that enolate·diisopropylamine complexes produce starting material via an internal return mechanism, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.
(15) ¹H−¹H EXSY NMR spectroscopy (297 K, CDCl₃) of **5** indicates that the conformers exchange at a rate of 0.2 s⁻¹ ($\Delta G^{\ddagger} = 18.5$ kcal/mol).
(16) Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748.
(17) (a) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694−9696. (b) Fuji, K.; Kawabata, T. *Chem.-Eur. J.* **1998**, *4*, 373−376. (c) Wanyoike, G. N.; Onomura, O.; Maki, T.; Matsumura, Y. *Org. Lett.* **2002**, *4*, 1875−1877. (d) Brewster, A. G.; Jayatissa, J.; Mitchell, M. B.; Schofield, A.; Stoodley, R. J. *Tetrahedron Lett.* **2002**, *43*, 3919−3922.
(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11.1; Gaussian, Inc.: Pittsburgh, PA, 2001.

JA0365781