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Highly Enantioselective Synthesis of Rigid, Quaternary 1,4-Benzodiazepine-2,5-diones Derived from Proline

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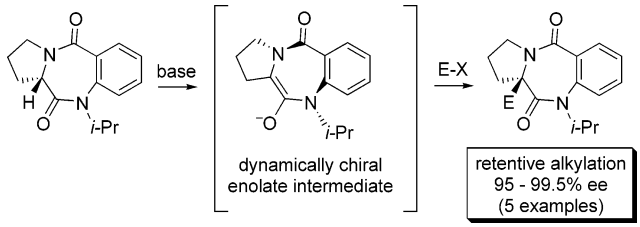
ABSTRACT



Proline-derived 1,4-benzodiazepine-2,5-diones are extremely useful scaffolds in medicinal chemistry. In this paper, we describe a protocol for retentive C3 alkylation of these materials, thus accomplishing the direct synthesis of enantiopure quaternary 1,4-benzodiazepine-2,5-diones. The high enantioselectivities (up to 99.5%) are attributed to memory of chirality.

1,4-Benzodiazepine-2,5-diones (BZDs) constitute a privileged structure that exhibits diverse biological activity.[1] In particular, proline-derived BZDs have shown promise as anxiolytic drug candidates (e.g., **1**, Figure 1) and as starting materials for the synthesis of anthramycin-inspired anticancer drugs (e.g., **2**),[2] DNA-cross-linking agents (e.g., **3**),[3] and α5-selective GABA(A) receptor ligands (e.g., **4**).[4] Despite the impressive diversity of BZDs prepared to date,[1c] examples possessing a quaternary stereogenic center at C3 have been largely unexplored,[5] likely due to the limited commercial availability of the corresponding enantiopure quaternary amino acids. Concerns that disubstitution at C3 would introduce conformational heterogeneity in the seven-

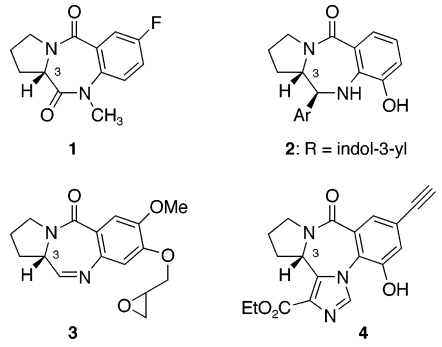


Figure 1. Medicinally important proline-derived 1,4-benzodiazepine-2,5-diones and derivatives.

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(2) Nagasaka, T.; Koseki, Y.; Hamaguchi, F. *Tetrahedron Lett.* **1989**, *30*, 1871−1872.

(3) Wilson, S. C.; Howard, P. W.; Forrow, S. M.; Hartley, J. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *J. Med. Chem.* **1999**, *42*, 4028−4041.

(4) Li, X.; Yu, J.; Atack, J. R.; Cook, J. M. *Med. Chem. Res.* **2004**, *13*, 259−281.

(5) The sole example of which we are aware is found in: Confalone, P. N.; Huie, E. M.; S. Ko, S.; Cole, G. M. *J. Org. Chem.* **1988**, *53*, 482−487.

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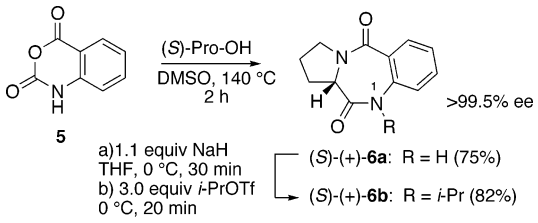
membered ring may have also discouraged exploration of quaternary BZDs.[6]

In this paper, we demonstrate the direct enantioselective synthesis of quaternary 1,4-benzodiazepin-2,5-diones. High enantioselectivities are achieved (up to 99.5%), and asymmetric induction is attributed to memory of chirality.[7,8] Finally, we demonstrate that these proline-derived quaternary BZDs rigidly retain a single conformation of the seven-membered ring.

Synthesis of the desired BZD starting material **6a** was accomplished by heating isatoic anydride **5** with (*S*)-Pro-OH (Scheme 1).[1a] Since enantioselective deprotonation/

Scheme 1. Synthesis of *N*1-*i*-Pr BZD (*S*)-(+)-**6b**

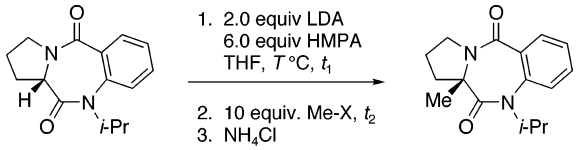


alkylation of 1,4-benzodiazepin-2-ones is facilitated by a large group at N1,[8a] an *i*-Pr group was installed at N1. Nonracemizing alkylation was achieved through the use of *i*-PrOTf;[9] chiral stationary-phase HPLC confirmed the enantiopurity of (*S*)-(+)-**6b**.

Treatment of (*S*)-**6b** with LDA (2.4 equiv) in THF at −78 °C for 5 min, followed by addition of MeI (10 equiv), afforded racemic **7b** in 22% yield (Table 1, entry 1).

However, by reducing the deprotonation time to 1 minute, **7b** was obtained in a promising 93% ee, but in only 10% yield (Table 1, entry 2). To improve enantioselectivity and chemical yield, the reaction temperature was lowered to −100 °C and MeOTf was employed as the electrophile. Using a 1 min deprotonation time and a 5 min reaction time, **7b** was obtained in >99.5% ee and 52% yield (Table 1, entry 3). Increased reaction times (10 and 15 min) improved the yield to 69 and 76%, respectively, but caused a slight deterioration of the asymmetric induction at the longer reaction time (95% ee at t_2 = 15 min). These results suggested the formation of a dynamically chiral enolate

Table 1. Evidence for a Dynamically Chiral Intermediate in the Enantioselective Deprotonation/Methylation of (*S*)-(+)-6b



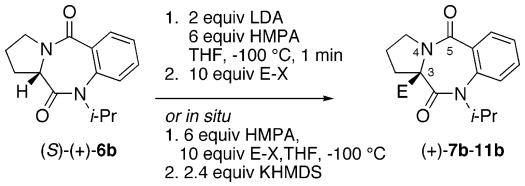
entry	Me-X	T (°C)	t_1 (min)	t_2 (min)	% yield	% ee[a]
1	MeI	−78	5	10	22	0
2	MeI	−78	1	10	10	93
3	MeOTf	−100	1	5	52	>99.5
4	MeOTf	−100	1	10	69	>99.5
5	MeOTf	−100	1	15	76	95

[a] Enantiomeric excess measured by chiral stationary-phase HPLC (Chiralcel AD).

intermediate that racemizes rapidly at −78 °C but more slowly at −100 °C.

Extension of this protocol to allyl and benzyl bromide gave the desired products **8b** and **9b** in 83 and 78% ee, respectively (Table 2, entries 2,4, "sequential" column). The

Table 2. Optimized Results for Sequential and in Situ Deprotonation/Alkylation of (*S*)-6b[a]



entry	E-X	product	sequential % ee[b] (yield)	in situ % ee[b] (yield)
1	MeOTf	(+)-**7b**	95 *S* (76)	>99.5 *S* (24)
2	allyl-Br	(+)-**8b**	83 (77)	98 (75)
3	allyl-I		99.5 (89)[c]	
4	BnBr	(+)-**9b**	78 *R* (64)	96 *R* (92)
5	BnI		93 *R* (77)	
6	4-MeBnBr	(+)-**10b**		99 *R*[d] (92)
7	4-MeBnI		95 *R*[d] (63)	
8	2-PhBnBr	(+)-**11b**		95 *R*[e] (82)
9	2-PhBnI		95 *R*[e] (63)	

[a] Reactions were complete within 15 min by TLC. [b] % ee measured by chiral stationary-phase HPLC (Chiralcel AD). Unless otherwise indicated, absolute stereochemistry was determined by chemical correlation (vide infra). [c] Reaction performed without added HMPA. [d] (*R*)-stereochemistry assigned to (+)-**10b** on the identical sign of rotation and HPLC elution order with simple benzyl analogue (*R*)-(+)-**9b**. [e] (*R*)-stereochemistry assigned to (+)-**11b** on the identical sign of rotation with simple benzyl analogue (*R*)-(+)-**9b**.

lower enantioselectivities relative to methylation again suggested competitive enolate racemization on the alkylation time scale. Reasoning that an improvement in the alkylation rate could reduce racemization, we repeated the alkylations

(6) Binding affinities at the GABA(A) receptor are exquisitely sensitive to the conformation (*M*- or *P*-) of the benzodiazepine ring, which is governed by the pseudoequatorial preference and absolute stereochemistry of the C3 substituent: (a) Konowal, A.; Snatzke, G.; Alebiš-Kolbah, T.; Kafješ, F.; Rendiš, S.; Šunjiæ, V. *Biochem. Pharmacol.* **1979**, *28*, 3109−3113. (b) Qi, H.; He, X.; Ma, C.; Liu, R.; Yu, S.; Dayer, C. A.; Wenger, G. R.; McKernan, R.; Cook, J. M. *J. Med. Chem.* **2000**, *43*, 71−95.

(7) (a) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373−376. (b) Kawabata, T.; Fuji, K., In *Topics in Stereochemistry*; Denmark, S. E., Ed.; John Wiley & Sons: New York, 2003; Vol. 23, pp 175−205. (c) Zhao, H.; Hsu, D.; Carlier, P. R. *Synthesis* **2005**, 1−16.

(8) We have previously published highly enantioselective deprotonation/alkylation reactions of the related 1,4-benzodiazepin-2-one scaffold: (a) Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 11482−11483. (b) Carlier, P. R.; Lam, P. C.-H.; DeGuzman, J. C.; Zhao, H. *Tetrahedron: Asymm*etry **2005**, *16*, 2998−3002.

(9) Beard, C. V.; Baum, K.; Grakaskas, V. *J. Org. Chem.* **1973**, *38*, 3673−3677.

using allyl iodide and benzyl iodide and obtained the desired products in 99.5 and 93% ee (Table 2, entries 3 and 5). Application of two substituted benzyl iodides in this protocol also gave excellent % ee and satisfactory yields (Table 2, entries 7 and 9).

We reasoned that the moderate alkylation yields attained in the 1 min deprotonation protocol might be due to incomplete enolate formation. Since lengthening the deprotonation time would increase the extent of enolate racemization, we sought conditions that would allow enolate to form in the presence of electrophile. Because this in situ protocol would also allow instantaneous trapping of the enolate, we anticipated an improvement in enantioselectivity. This in situ strategy has been successfully applied to the synthesis of quaternary Ala-derived *N*-PMB 1,4-benzodiazepin-2-ones.[8b] An obvious key requirement for this protocol is that the base (present in excess) not react with the electrophile at −100 °C. This requirement was met through the use of KHMDS[8b] and allylic and benzylic bromides (rather than iodides). As can be seen in Table 2, application of the in situ protocol for reaction of allyl bromide gave significantly improved enantioselectivity (Table 2, entry 2, cf. "sequential" and "in situ" columns).

Similarly, the in situ protocol for benzylic bromides generally gave higher yields and enantioselectivities than the sequential protocol with the corresponding iodides (Table 2, cf. entries 4 and 5, 6 and 7, 8 and 9). Finally, application of the in situ protocol to methylation gave very poor yields, suggesting competitive reaction of KHMDS with MeOTf (Table 2, entry 1, cf. "sequential" and "in situ" columns). In summary, for methylation and allylation, the sequential 1 min LDA protocol is recommended. In all other cases, the in situ KHMDS protocol gives superior yields (75−92%) and enantioselectivity (95−>99.5% ee).

As was the case for Ala- and Phe-derived 1,4-benzodiazepin-2-ones,[8] the deprotonation/alkylation of **6b** appears uniformly retentive. The absolute configurations of (+)-**7b** and **9b** were determined by hydrolysis to the known quaternary amino acids, (*S*)-(−)-α-Me-Pro-OH and (*R*)-(−)-α-Bn-Pro-OH. Retentive (*R*)-stereochemistry is assigned to (+)-**10b** and (+)-**11b** based on the positive rotation of (*R*)-**9b**. ^{1}H and ^{13}C NMR spectroscopy of **7b**−**11b** indicate a single conformation of the BZD ring, in sharp contrast to quaternary 1,4-benzodiazepin-2-ones, which exist as mixtures of the (*M*)- and (*P*)-conformers.[8,10,11] B3LYP/6-31G* calculations[12] of the possible equatorial proline (*M*)-(*S*)- and axial proline (*P*)-(*S*)-conformations of **7b** indicate a 25.8 kcal/mol preference for the former at 25 °C. This strong preference is due in large part to amide resonance, which is retained in the equatorial-proline (*M*)-(*S*)-conformation, but compromised in the axial-proline (*P*)-(*S*)-conformation (O−C5−N4−C3 dihedrals of −174.6 and −73.7°, respectively).

Successful memory of chirality transformation requires the formation of an enantiopure conformationally chiral reactive intermediate that racemizes slowly on the reaction time scale.[7c] To account for formation of an enantiomerically pure enolate from (*S*)-**6b**, we have computationally modeled its reaction with dimeric lithium dimethylamide. Dimer-based mechanisms for deprotonation of ketones and esters by LDA and LiHMDS have been identified experimentally,[13] and open dimer mechanisms for deprotonation of ketones have been studied computationally.[14] Transition structures leading to the (*M*)- and (*P*)-enolates were located at B3LYP/6-31G*; single-point energies were calculated at B3LYP/6-31+G* (Figure 2). Transition state (*M*)-(*S*)-**12b** leading to the (*M*)-enolate is favored by 11.9 kcal/mol (173 K). Examination of the corresponding explicit bis(Me_2O) solvates (*M*)-(*S*)- and (*P*)-(*S*)-**13b** similarly indicated a 9.7 kcal/mol (173 K) preference for formation of the (*M*)-enolate. Thus, the formation of an enantiopure (*M*)-enolate by deprotonation of (*S*)-**6b** appears feasible.

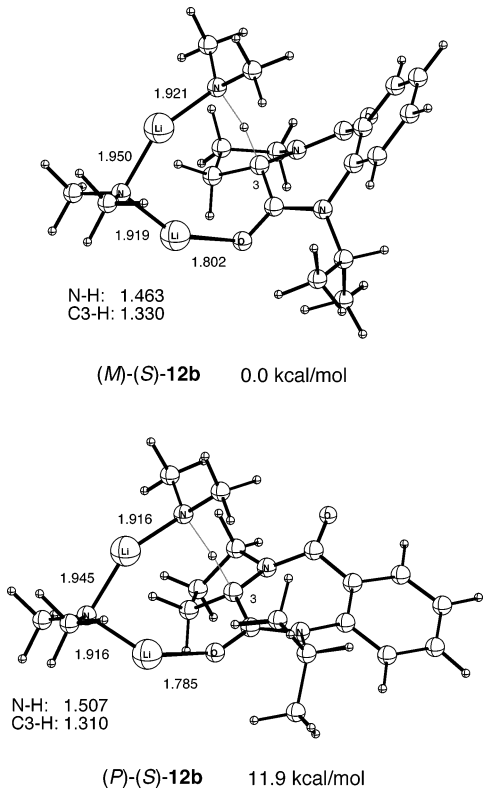


Figure 2. B3LYP/6-31G* transition structures for deprotonation of (*S*)-**6b** by $(LiNMe_2)_2$. Selected bond lengths in Å; relative free energies at B3LYP/6-31+G*.

Because the solution structure of the enolate intermediate derived from (*S*)-**6b** is not yet known, we considered two limiting structures: free anion (*M*)-**14b** and the corresponding $Li(OMe_2)_3$ salt (*M*)-**15b**. Both the equilibrium geometries of these species and their corresponding ring-inversion transition structures **14b*** and **15b*** were located at B3LYP/6-31G* (Figure 3). B3LYP/6-31+G*//B3LYP/6-31G* activation free energies for racemization of **14b** and **15b** are 12.2 and 16.0 kcal/mol, corresponding to racemization half-

(10) Lam, P. C.-H.; Carlier, P. R. *J. Org. Chem.* **2005**, *70*, 1530−1538.

(11) We use the helical descriptors (*M*)- and (*P*)- to assign the chirality of the ring, according to the sign of the C2−N1−C7−C6 dihedral angle (*M* = minus, *P* = positive).

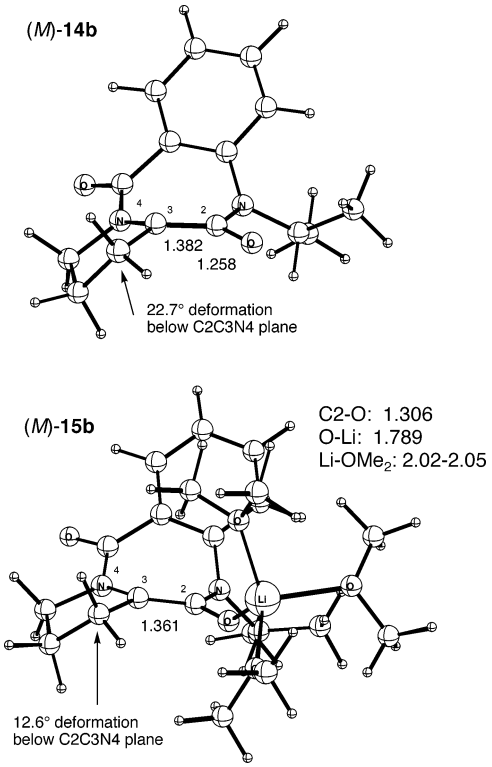


Figure 3. B3LYP/6-31G* equilibrium geometries for enolate free anion (*M*)-**14b** and its $Li(OMe_2)_3$ salt (*M*)-**15b**. Selected bond lengths in Å.

lives of 4 min and 180 days, respectively (173 K). Thus, it appears that enolates derived from **6b** would have sufficient conformational stability to react in situ at −100 °C without significant racemization. Alkylation of the (*M*)-enolate from the top face would then afford retentive products (*S*)-**7b** and (*R*)-**8b**−**11b**. The factors favoring this contra-steric concave face alkylation are currently under study. However, we note that the enolates **14b** and **15b** are slightly pyramidalized at C3: the attached proline CH_2 carbon in these structures is deformed 22.7 and 12.6° below the C2C3N4 plane. Thus, C3 in the enolate is pyramidalized toward the favored trajectory for electrophilic attack.[15]

In conclusion, we have developed a concise, highly enantioselective route to proline-derived quaternary BZDs. These compounds adopt a rigid conformation of the benzodiazepine ring and should be useful intermediates for the synthesis of hitherto inaccessible analogues of important BZD-based drugs. Strategies that allow diverse subsitution at N1 are under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures, analytical data, calculated structures, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Gaussian 03, Revision B.05: Frisch, M. J.; Trucks, G. W.; Schlegal, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pompelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B. ; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 2003.

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