

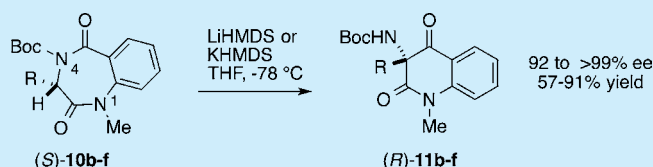
Enantioselective Deprotonative Ring Contraction of N1-Methyl-N4-Boc-benzo[*e*][1,4]diazepine-2,5-diones

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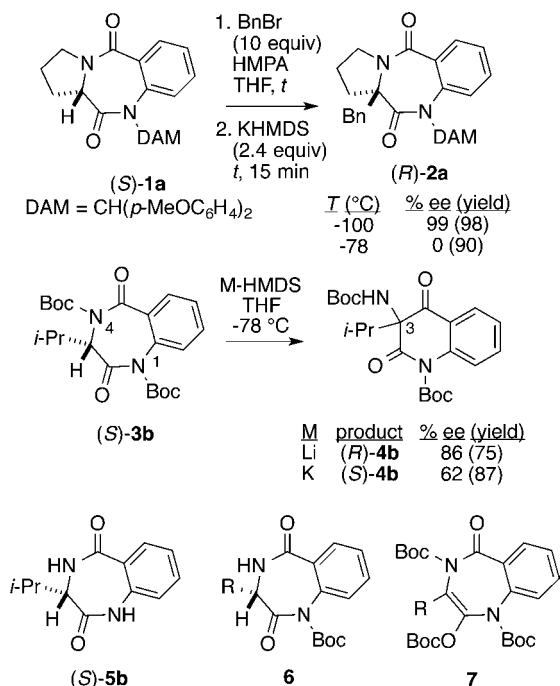
S Supporting Information

ABSTRACT: N1-Methyl-N4-Boc-benzo[*e*][1,4]diazepine-2,5-diones were prepared in good yield and high stereochemical purity from five amino acids. Upon deprotonation, these compounds undergo ring contraction to the corresponding quinolone-2,4-diones with high enantioselectivity, providing efficient entry to a potentially useful drug scaffold. Mechanistic commentary and comparisons to related reactions are provided.



Benzo[*e*][1,4]diazepine-2,5-diones feature prominently in medicinal chemistry,¹ and we have previously reported enantioselective synthetic methods to increase available diversity within this scaffold.² Deprotonation of Pro-derived (*S*)-**1a** at $-100\text{ }^{\circ}\text{C}$ in the presence of carbon electrophiles gives quaternary benzodiazepine-2,5-diones such as (*R*)-**2a** in high yield and enantiomeric excess (Scheme 1). If this reaction is performed at a warmer temperature ($-78\text{ }^{\circ}\text{C}$), racemic **2a** is obtained, suggesting the intermediacy of a quickly racemizing,

Scheme 1. Enantioselective Deprotonation/Alkylation² and Deprotonative Ring-Contraction³ Reactions of Benzo[*e*][1,4]diazepine-2,5-diones

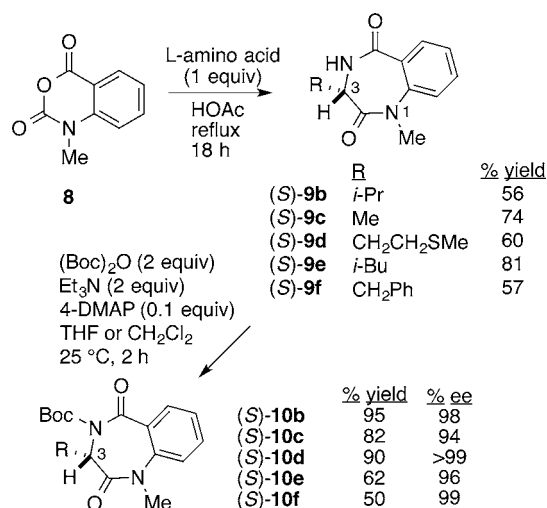


axially chiral enolate. Recently Dewynter reported that deprotonation of a Val-derived (*S*)-**3b** in the absence of an electrophile resulted in enantioselective ring contraction to **4b**.³ Interestingly, LiHMDS and KHMDS were found to give enantiomeric products, in 86% and 62% ee, respectively. This ring contraction constitutes an example of the acyl-amino variant of the Chan reaction,⁴ and a related transformation of a benzodiazepine-2,5-dione affording achiral products has been recently disclosed.⁵ We were intrigued by the enantiodivergent paths taken by the Li and K enolates derived from (*S*)-**3b**, as well as the potential usefulness of 3,3-disubstituted quinoline-2,4-diones such as **4b** as drug scaffolds.⁶ Unfortunately, (*S*)-**3b** was the only substrate investigated in this reaction. Whereas Val-derived (*S*)-**5b** was easily transformed to the N1, N4-di-Boc derivative (*S*)-**3b**, the same transformation was not possible with substrates derived from L-Ala, Ile, Phe, and phenylglycine; in these reactions only mono- and tri-Boc derivatives **6** and **7** were obtained.³

To improve the scope and enantioselectivity of this deprotonative ring contraction we explored replacing the N1-Boc substituent of the ring-contraction substrates with an alkyl group. Based on the proposed mechanism of the acylamino variant of the Chan reaction,^{4b} only N4 would require activation by an acyl group to facilitate the desired ring contraction. Thus, L-Val, Ala, Met, Leu, and Phe were reacted with *N*-methylisatoic anhydride **8** in acetic acid at reflux, affording N1-Me benzo[*e*][1,4]diazepine-2,5-diones (*S*)-**9b–f** (Scheme 2). Partial racemization occurred in these reactions, and the moderate to good yields reported for **9b–f** reflect recrystallization to improve enantiomeric enrichment. This strategy worked well for all compounds except **9f**, which was not highly crystalline; in this case final enantiomeric enrichment was carried out by recrystallizing the N4-Boc derivative **10f**.

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Scheme 2. Preparation of Ring-Contraction Reaction Substrates (S)-10b–f


Interestingly, in the case of Met-derived **9d**, the racemate crystallized out of solution, and the enantiomerically pure material remained in solution. Installation of a single Boc group on (S)-**9b–f** was not problematic, and derivatives (S)-**10b–f** were prepared in moderate to excellent yields and in 94 to >99% ee.

The NMR spectra of (S)-**9b–f** are easily interpreted and are consistent with one predominant conformation. Based on our previous studies of 3-substituted benzodiazepine-2-ones,⁷ we expected the C3-substituent to adopt a pseudoequatorial orientation, and X-ray crystallography demonstrates this conformation for (±)-**9d** (Figure 1). In contrast, with the

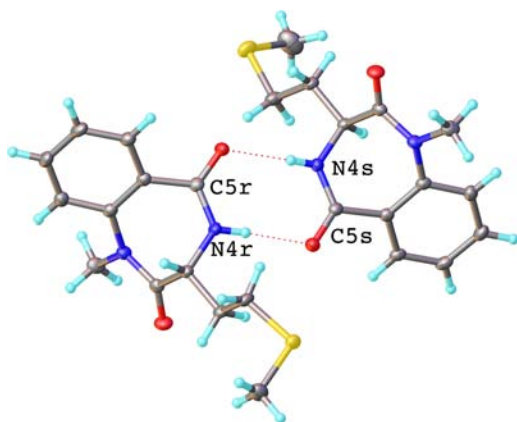


Figure 1. Anisotropic ellipsoid drawing (50%) of (±)-**9d**. The left and right molecules are (R)- and (S)-configured, respectively. Figure generated using OLEX2.⁸

exception of (S)-**10b**, the room temperature NMR spectra of the N4-Boc derivatives (S)-**10** are broad and often difficult to interpret. We speculated that these compounds exist as slowly interconverting mixtures of pseudoaxial and -equatorial conformers (Figure 2). We have previously demonstrated such conformational isomerism in 3,3-disubstituted (“quaternary”) benzodiazepine-2-ones,^{2b,7} and this conformation mobility was invoked to explain the stereochemical course of ring contractions of related substrate (S)-**3b**.³

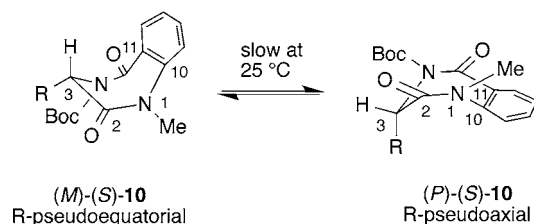


Figure 2. Conformational isomerism in **10**. Axial chirality descriptors (M)- and (P)- are determined by the sign of the C2–N1–C10–C11 dihedral.^{7c}

Consistent with this proposal, NMR spectroscopy of (S)-**10c–f** at 0 °C accomplished decoalescence, demonstrating doubling of most nuclei in each compound. In addition, X-ray crystallographic analysis of (S)-**10e** remarkably shows both conformers in the unit cell: the R-pseudoequatorial (M)-conformer is well-resolved, but the R-pseudoaxial (P)-isomer is partly disordered (Figure 3).

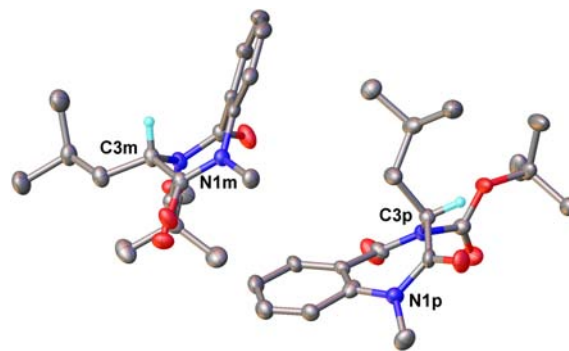
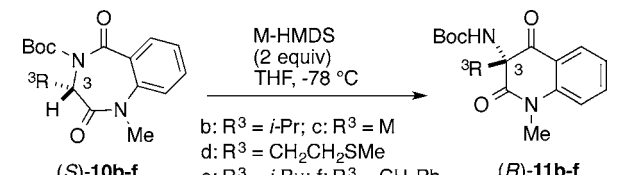


Figure 3. Anisotropic ellipsoid drawing (50%) of (S)-**10e**. Both (M)- and (P)-conformations are present in the unit cell, with the *i*-Bu substituents in the pseudoequatorial and pseudoaxial positions, respectively. Except at C3, hydrogens are omitted for clarity. The (P)-conformer (right) is partly disordered: the major (66%) orientation is shown here, and the minor orientation (34%) is shown in the Supporting Information.

With the desired substrates (S)-**10b–f** in hand we carried out deprotonations with LiHMDS and KHMDS in THF (Table 1). As can be seen, reaction of (S)-**10b** with both bases gave the desired ring-contracted product (–)-**11b** in good yield and excellent enantioselectivity (98% ee). Furthermore, chiral stationary phase HPLC indicated that both bases gave the same major enantiomer, contrary to the published observations of (S)-**3b** (Scheme 1).³ This levorotatory product was crystallized, and anomalous dispersion indicated (R)-configuration (Supporting Information). Reactions of (S)-**10c–f** proceeded similarly in moderate to good yields and good to excellent enantioselectivities. Again, in each case, reactions with LiHMDS and KHMDS gave the same major enantiomer. In the case of **10c** and **10e**, KHMDS gave superior enantioselectivity; for **10f**, LiHMDS proved optimum. Only in the case of (S)-**10e** (KHMDS, 92% ee) was greater than 95% ee not attained. The absolute configurations of the products **11c–f** derived from (S)-**10c–f** are all deduced to be (R)- by analogy, supported by two additional observations. First, the major enantiomers of **11b–f** derived from (S)-**10b–f** are uniformly first-eluting on Chiralcel OD HPLC. Second, in each case the sign of optical rotation of the products conforms to that of the starting materials.

Table 1. Deprotonative Ring-Contraction Reactions

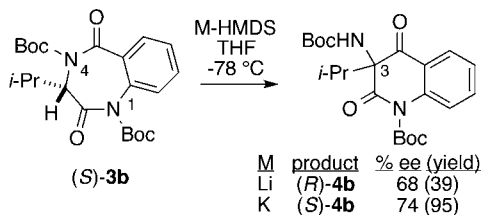


entry	substrate	M	product	yield	% ee (config)
1	(S)-(-)-10b	Li	(-)-11b	84	98 (R) ^a
2	(S)-(-)-10b	K	(-)-11b	84	98 (R) ^a
3	(S)-(+)-10c	Li	(+)-11c	69	92 (R) ^b
4	(S)-(+)-10c	K	(+)-11c	57	97 (R) ^b
5	(S)-(-)-10d	Li	(-)-11d	91	>99 (R) ^b
6	(S)-(-)-10d	K	(-)-11d	63	>99 (R) ^b
7	(S)-(-)-10e	Li	(-)-11e	56	84 (R) ^b
8	(S)-(-)-10e	K	(-)-11e	58	92 (R) ^b
9	(S)-(-)-10f	Li	(-)-11f	85	98 (R) ^b
10	(S)-(-)-10f	K	(-)-11f	82	92 (R) ^b

^aThe absolute configuration of (-)-11b was established as (R)- by X-ray crystallography (Supporting Information). ^bThe products of rearrangement of (S)-10c–f (11c–f) are assigned an (R)-configuration based on HPLC elution order and conformity of optical rotation (in every case the sign of rotation is preserved from (S)-10b–f to products 11b–f).

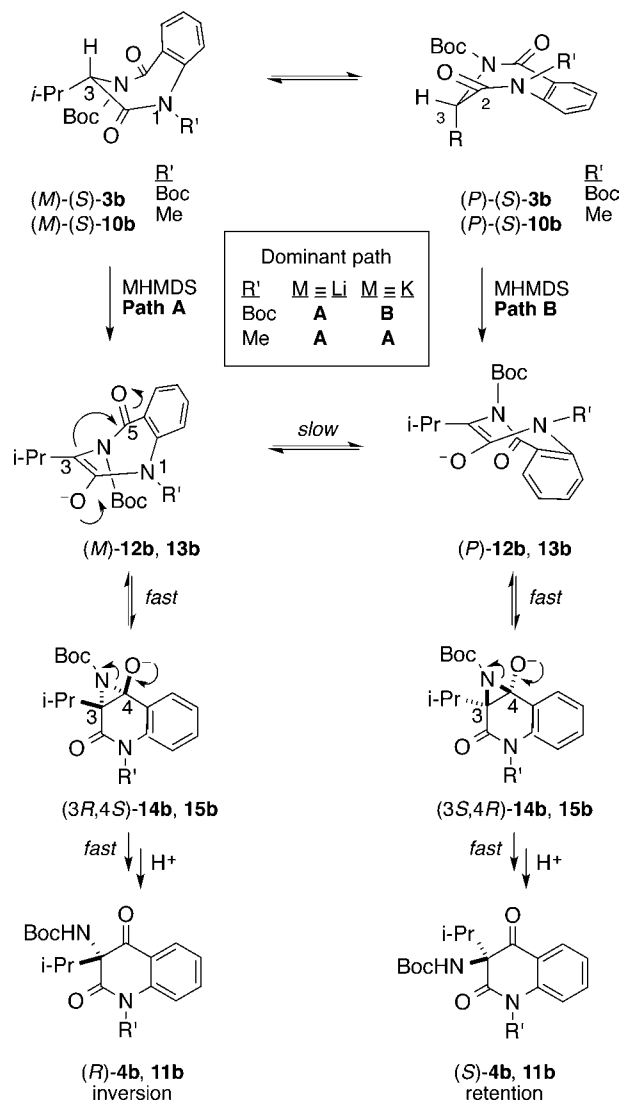
Since the N1-Me, N4-Boc substrates (S)-10b–f gave (R)-configured ring-contraction products 11b–f regardless of whether LiHMDS or KHMDS was used, we thought it prudent to independently confirm the literature reactions of (S)-3b. Following a slight modification of the original procedure, we prepared (S)-3b and subjected it to both bases (Scheme 3).

Scheme 3. Confirmation of Enantiodivergent Outcomes in Reactions of (S)-3b (97% ee) with LiHMDS and KHMDS



As reported by Dewynter and co-workers,³ we found that deprotonation of (S)-3b with LiHMDS gave (R)-(-)-4b, and deprotonation with KHMDS gave (S)-(+)-4b. Comparing the different outcomes of related substrates (S)-3b and (S)-10b with KHMDS, it is clear the identity of the N1 substituent plays a major role in the stereochemical course of these reactions.

How can the enantiodivergent outcomes of (S)-3b with LiHMDS and KHMDS be reconciled with the uniform (R)-selectivity seen in reactions of (S)-10b–f? In the case of (S)-3b, Dewynter and co-workers proposed that deprotonation of both (M)- and (P)-conformers could occur, with LiHMDS favoring the former, and KHMDS the latter³ (Scheme 4). As can be seen, the C3 protons of (M)-(S)-3b and (M)-(S)-10b are pseudoaxial and appear stereoelectronically well-disposed for deprotonation, as we have established in studies of related benzodiazepin-2-ones.^{2b,7a,c,9} In contrast the C3 protons of (P)-(S)-3b and (P)-(S)-10b are pseudoequatorial and deprotonation appears difficult because of poor overlap between the C3–H σ and the C2–O π^* .

Scheme 4. Possible Stereochemical Pathways for Deprotonation of (S)-3b and 10b (Adapted from Dewynter³)

Thus, for any given base we would normally expect that pseudoaxial deprotonation (Path A) to dominate, leading to the observed invertive course of reaction seen for (S)-3b with LiHMDS and that for (S)-10b with both bases.

To account for pseudoequatorial deprotonation of (S)-3b by KHMDS (Path B) would require detailed computational studies of possible transition structures. Nevertheless, comparison of the solid-state structures of the substrates involved might provide a clue as to how a Path B deprotonation of (S)-3b might be more favorable than that of (S)-10b–f. To that end an X-ray quality crystal of (S)-3b was obtained, which demonstrated that the C3-substituent adopts a pseudoaxial conformation (Figure 4). So the (P)-conformation of (S)-3b required for Path B deprotonation is readily accessible or even preferred, as suggested by previous calculations.³ The structures of (M)-(S)-10e, (P)-(S)-10e, and (P)-(S)-3b were then compared. In all three structures sp^2 -hybridization at N was indicated by the sum of angles at N1 and N4 ($\theta \geq 357.9^\circ$, Supporting Information). However, these structures differ in the extent of amide resonance within, and external to, the benzodiazepine ring. We assessed the extent of resonance by

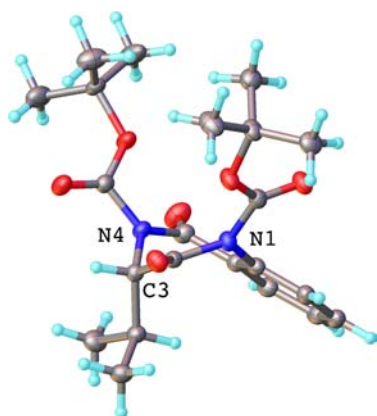


Figure 4. Anisotropic ellipsoid drawing (50%) of (S)-3b.

examining amide twist torsion angles τ^{10} along the N1–C2, N4–C5, N4–C15, and N1–C12 bonds (where applicable, see Table 2). For (S)-10e (both conformers), values of τ_{1-2} and

Table 2. Select Torsion Angles for (S)-10e and (S)-3b^a

	(M)-(S)-10e	(P)-(S)-10e ^b	(P)-(S)-3b
R'	Me	Me	Boc
R	<i>i</i> -Bu	<i>i</i> -Bu	<i>i</i> -Pr
τ_{1-2}	4.7 ± 0.4°	−13.5 ± 1.8°	−36.4 ± 0.3°
τ_{4-5}	3.4 ± 0.4°	−16.7 ± 0.9°	−31.9 ± 0.4°
τ_{4-15}	−45.6 ± 0.4°	−39.6 ± 0.7°	−19.4 ± 0.3°
τ_{1-12}	na	na	3.3 ± 0.3°
HC3C2O13	132.8 ± 0.2°	15.2 ± 1.3°	21.6 ± 0.2°

^aError in torsion angles calculated from ESDs (Supporting Information). ^bThe (P)-conformer of (S)-10e is disordered; torsion angles are listed for the major orientation (see Figure 3).

τ_{4-5} are much closer to zero than are the values of τ_{4-15} , indicating endocyclic amide resonance (N1–C2, N4–C5) is more important than exocyclic (N4–C15) amide resonance (Table 2). However, in (P)-(S)-3b the situation is reversed: the exocyclic amide resonance of N1 and N4 with their attached Boc groups is stronger than that within the ring (cf. τ_{1-12} and τ_{1-2} , τ_{4-15} and τ_{4-5} , Table 2).

Reduced endocyclic amide resonance for 3b compared to 10b–f suggests greater flexibility of 3b along the N1–C2 and N4–C5 axes. Thus, stereoelectronically acceptable HC3C2O13 torsion angles might be more easily obtained in the KHMDS deprotonation of (P)-(S)-3b than that of (P)-(S)-10b–f. In the solid state the HC3C2O13 torsion angle for (P)-(S)-3b is indeed larger than that of (P)-(S)-10e (21.6° vs 15.2°).

In conclusion we have repeated the findings of Dewynter and co-workers³ on deprotonation of (S)-3b and found that, by replacing the N1-Boc group by an alkyl group (Me), a wider variety of ring-contraction substrates may be prepared. Unlike (S)-3b, deprotonations of (S)-10b–f are (R)-selective with both LiHMDS and KHMDS. Enantioselective ring contractions of (S)-10b–f occur in higher enantiomeric excess than that of (S)-3b, potentially opening a route to diversely functionalized

enantioenriched 3-amino-3-alkylquinolone-2,4-diones 11. Work is in progress to further expand the scope of this reaction as well as to better understand the enantiodivergent outcomes of (S)-3b.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, analytical data, chromatograms, NMR spectra, X-ray structure of (R)-11b, and .cif files for (S)-3b, (±)-9d, (S)-10e, and (R)-11b. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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