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# Enantioselective Synthesis of Diversely Substituted Quaternary 1,4-Benzodiazepin-2-ones and 1,4-Benzodiazepine-2,5-diones

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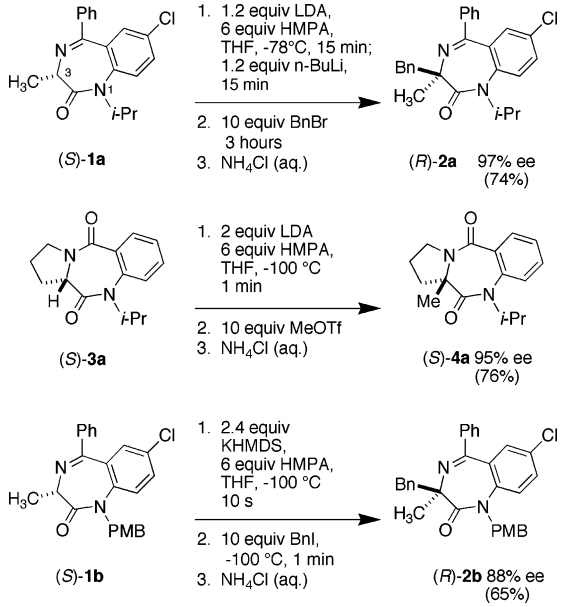
***Abstract:*** Benzodiazepines are privileged scaffolds in medicinal chemistry, but enantiopure examples containing quaternary stereogenic centers are extremely rare. We demonstrate that installation of the di-(*p*-anisyl)methyl (DAM) group at N1 of 1,4-benzodiazepin-2-ones and 1,4-benzodiazepine-2,5-diones derived from enantiopure proteinogenic amino acids allows retentive replacement of the C3-proton via a deprotonation/trapping protocol. A wide variety of carbon and nitrogen electrophiles function well in this reaction, providing the corresponding quaternary benzodiazepines with excellent enantioselectivity. Deprotonation/trapping experiments on a pair of diastereomeric 1,4-benzodiazepine-2,5-diones provide evidence for a key role of conformational chirality in these enantioselective reactions. Acidic removal of the DAM group is fast and high-yielding and can be performed selectively in the presence of a *N*-Boc indole. Thus the synthesis of quaternary benzodiazepines with diverse N1 functionality can now be accomplished.

## Introduction

Benzodiazepines are privileged scaffolds in medicinal chemistry,[1] prompting the development of combinatorial methods for the synthesis of 1,4-benzodiazepin-2-ones,[2] 1,4-benzodiazepine-2,5-diones,[3] and related heterocycles.[4,5] Since α-amino acids are the key starting materials that supply the configuration at C3 in these heterocycles, it is not surprising that benzodiazepines featuring a quaternary stereogenic center at C3 have received little attention. To provide a concise synthesis of these compounds we developed enantioselective deprotonation/alkylation routes to quaternary 1,4-benzodiazepin-2-ones[6] and proline-derived 1,4-benzodiazepine-2,5-diones.[7] Treatment of (*S*)-**1a** with base at −78 °C, followed by addition of benzyl bromide, gives (*R*)-**2a** in 97% ee with retention of configuration (Scheme 1). A similar sequence applied to (*S*)-**3a** at −100 °C gives quaternary 1,4-benzodiazepine-2,5-dione (*S*)-**4a** in 95% ee. The high enantioselectivities observed in these reactions are attributed to "memory of chirality":[8−10] deprotonation destroys the $sp^3$-hybridized stereogenic center of the starting materials but generates an enantiopure, conformationally chiral enolate that racemizes slowly on the alkylation reaction time scale. The requirement for an *i*-Pr group at N1 in these reactions clearly limits the appeal of this methodology, since this group cannot

***Scheme 1.*** Enantioselective Deprotonation/Alkylation of 1,4-Benzodiazepin-2-ones and 1,4-Benzodiazepine-2,5-diones

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(10) The term chirality in the phrase "memory of chirality" originally coined by Fuji (Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694−9696) properly refers to the *sense* of chirality, or configuration. Chirality is retained in the intermediates whether they racemize or remain enantiopure; the same is obviously true of the products. Perhaps a better term would be "memory of configuration".

be easily removed. However, we have shown that a large N1-substituent is required for excellent enantioselectivities at −78 °C;[6,11] compound (*S*)-**1b**, which features a smaller but potentially replaceable PMB substituent at N1, requires the use of undesirable, cryogenic reaction temperatures (−100 to −109 °C) to achieve adequate enantioselectivity for deprotonation/alkylation.[11] Therefore, to allow the enantioselective synthesis of quaternary 1,4-benzodiazepin-2-ones and 1,4-benzodiazepine-2,5-diones that feature diverse N1 substitution, we sought to employ a bulky (secondary) N1 substituent that could be easily removed after the enantioselective deprotonation/alkylation step. In this paper we report that the di-(*p*-anisyl)methyl (DAM) group ably fills this role, providing quaternary benzodiazepines in higher enantioselectivities and yields than previously attained with the *i*-Pr and PMB substituents. Following deprotonation/alkylation, the DAM group can be removed with mild acid, providing the corresponding *N*-H quaternary benzodiazepines that can then be further functionalized at N1.

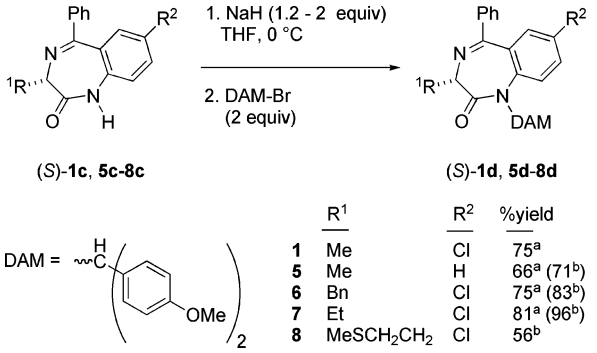
## Results and Discussion

We envisioned an ideal N1-substituent for enantioselective deprotonation/alkylation of 1,4-benzodiazepin-2-ones and 1,4-benzodiazepine-2,5-diones to have three characteristics. First, it must have steric bulk comparable to a secondary alkyl group, so that the derived enolate would not readily racemize at −78 to −100 °C. Second, it must be installed on the *N*-H precursor through the use of a highly reactive donor, since we have shown that reaction at 0 °C within hours is necessary to prevent racemization during N1 alkylation.[6] Last, a nonreductive deprotection was required due to the reductive sensitivity of the imine moiety in 1,4-benzodiazepin-2-ones. After exploration of several alternatives, only the DAM group filled these requirements.

DAM is a well-known protecting group for $\beta$-lactam amides[12,13] but has been less commonly used for larger lactams and acyclic amides.[14,15] In our hands, yields of the *N*-DAM amides proved critically dependent upon the purity of the DAM-Br.[16] The best procedure involved treatment of the corresponding alcohol (DAM-OH) with acetyl bromide in dry benzene at room temperature, removal of the reactants in vacuo, and recrystallization from hexane.

Syntheses of the *N*-DAM-1,4-benzodiazepin-2-ones (*S*)-**1d**, **5d**−**8d** are described in Scheme 2. *N*-H-1,4-Benzodiazepin-2-ones **1c**, **5c**−**8c** were prepared from the corresponding *N*-Boc amino acids and 2-aminobenzophenones by a modification of Shea's protocol[17] that we have previously described.[11] DAM-Br reacted with the sodium salts of (*S*)-**1c**, **5c**−**8c** within 2−4 h at 0 °C to give the corresponding *N*-DAM derivatives (*S*)-**1d**, **5d**−**8d** in good yield and typically >98% ee. Although deprotonation with 1.2−1.5 equiv of NaH gave good yields (66−81%), in several cases, the use of 2 equiv of NaH gave slightly higher yields and had no deleterious impact on enantiopurity of the *N*-DAM product. Note that benzhydryl bromide proved unreactive toward the sodium salt of **1c** under these conditions, even in the presence of HMPA.

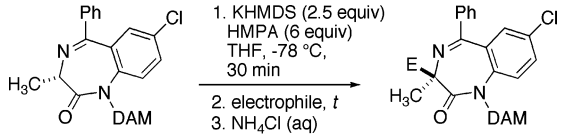
***Scheme 2.*** Synthesis of *N*-DAM-1,4-Benzodiazepin-2-ones (*S*)-**1d**, **5d**−**8d**




| | $R^1$ | $R^2$ | %yield | %ee |
|---|---|---|---|---|
| **1** | Me | Cl | 75[a] | >99.5 |
| **5** | Me | H | 66[a] (71[b]) | >99.5 |
| **6** | Bn | Cl | 75[a] (83[b]) | >99.5 |
| **7** | Et | Cl | 81[a] (96[b]) | 94 |
| **8** | $MeSCH_2CH_2$ | Cl | 56[b] | 98 |

[a] 1.2 equiv of NaH (**5d**−**7d**) or 1.5 equiv of NaH (**1d**) was used. [b] 2.0 equiv of NaH was used.

***Table 1.*** Enantioselective Deprotonation/Alkylation of Ala-Derived *N*-DAM-1,4-Benzodiazepin-2-one (*S*)-**1d** at −78 °C




| entry | E[a] | product | *t* (h) | % yield[b] | % ee[c] |
|---|---|---|---|---|---|
| 1 | Bn | (−)-**2d** | 4 | 80 (72) | 99 (97) *R* |
| 2 | 4-$MeC_6H_4CH_2$- | (−)-**9d** | 6 | 82 (76) | >99.5 (94) *R*[d] |
| 3 | *N*-Boc-indol-3-yl-$CH_2$- | (−)-**10d** | 4 | 96 | >99.5 |
| 4 | allyl | (+)-**11d** | 4 | 88 (76) | 99 (94) |
| 5 | $EtO_2CCH_2$- | (−)-**12d** | 2 | 86[e] (0) | 98 (na) *R* |
| 6 | Et | (+)-**13d** | 5 | 65[e,f] (0) | 96 (na) |
| 7 | -CN | (+)-**14d** | 0.16 | 95[e] | 99 |
| 8 | $N_3$ | (+)-**15d** | 0.5 | 88 | >99.5 |
| 9 | -N(Boc)-NHBoc | (−)-**16d** | 0.16 | 94 | >99.5 |

[a] Electrophiles (equiv) used: BnBr (10), 4-$MeC_6H_4CH_2Br$ (10), *N*-Boc-indol-3-ylmethyl bromide (2.5), allyl bromide (10), $BrCH_2CO_2Et$ (10), EtI (20), tosyl cyanide (2.0), trisyl azide (2.5), BocN=NBoc (5). [b] The yield in parentheses corresponds to that of the *N*-*i*-Pr analogue obtained from (*S*)-**1a**.[6] [c] Enantiomeric excess was measured by chiral stationary-phase HPLC; value in parentheses corresponds to that of the *N*-*i*-Pr analogue obtained from (*S*)-**1a**.[6] Where indicated, absolute stereochemistry was determined by correlation; retentive substitution is assumed by analogy in other cases. [d] (*R*) Stereochemistry of (−)-**9d** was deduced on the basis of similar sign of rotation and HPLC elution order compared to (−)-**2d**. [e] The benzodiazepine enolate was added to the electrophile. [f] LDA provided superior yields of **13d** and was used in place of KHMDS.

Use of our original protocol (LDA/*n*-BuLi/HMPA/THF) for deprotonation/alkylation of (*S*)-**1d** gave the desired products, but only in fair to moderate yields. After examination of a range of bases, the KHMDS protocol employed for *N*-PMB derivative **1b**[11] was found to provide both operational simplicity and superior yields. Results with alanine- (Ala-) derived 1,4-benzodiazepin-2-one (*S*)-**1d** are shown in Table 1.

Treatment of (*S*)-**1d** with KHMDS for 30 min in THF/HMPA at −78 °C produces an enolate that reacts well with a range of active carbon electrophiles (entries 1−4). Compared to our published deprotonation/alkylations of *N*-*i*-Pr analogue (*S*)-**1a**, both yields and enantioselectivities are significantly improved (cf. entries 1, 2, and 4). Enantioselectivities exceed 98%, and chemical yields range from 80% to 96%. The advantages of the DAM group are also evident in reaction with ethyl

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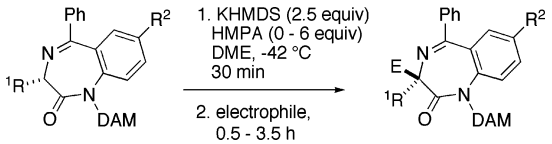
bromoacetate and ethyl iodide (entries 5−6), where the corresponding alkylations of the *N*-*i*-Pr analogue (*S*)-**1a** failed. In these cases, inverse addition of the enolate to the electrophile also proved important. Reaction with the sp-hybridized carbon electrophile tosyl cyanide[18] introduces the CN group in 95% yield and 99% ee (entry 7). Racemic glycine-derived 3-cyano-1,4-benzodiazepin-2-ones have been evaluated as antianxiety agents,[19] but to the best of our knowledge, quaternary 3-cyano-1,4-benzodiazepin-2-ones are heretofore unknown. Similarly, nitrogen functionalization at C3 is quite common in 1,4-benzodiazepin-2-one cholecystokinin antagonists,[1] Ras farnesylation inhibitors,[20] and antiarrhythmic agents,[21] but quaternary examples have not been described. Knowing that the potassium enolate of a glycine-derived 1,4-benzodiazepin-2-one undergoes azidation[21] with trisyl azide,[22] we explored use of this reagent. As can be seen in Table 1 (entry 8), excellent yield and enantioselectivity were obtained. Furthermore, reaction of the potassium enolate with of (*S*)-**1d** with di-*tert*-butyl azodicarboxylate[23] gave the corresponding protected hydrazine in excellent yield and enantioselectivity (Table 1, entry 9). We propose that the stereochemistry of the deprotonation/alkylation reactions depicted in Table 1 is uniformly retentive, based on correlation of (−)-**2d**, (−)-**9d**, and (−)-**12d** to the corresponding quaternary amino acids (vide infra).

Extension of this protocol to 1,4-benzodiazepin-2-ones derived from other amino acids was then performed. Unexpectedly, yields with phenylalanine- (Phe-), aminobutyric acid- (Abu-), and methionine- (Met-) derived 1,4-benzodiazepin-2-ones were low, suggesting that steric hindrance in the enolate was slowing alkylation. After considerable experimentation we found that preparation of the enolates in DME at −42 °C (acetonitrile/$CO_2$) and inverse addition to the electrophile gave acceptable yields without significantly reducing enantioselectivity (Table 2).

As a first example of this modified protocol we present Ala derivative (*S*)-**5d**, which lacks the 7-chloro substituent present in **1d** and all our previously published substrates.[6,11,24] With benzyl bromide as the electrophile, (*S*)-**5d** gave the desired product in 78% yield and 98% ee (Table 2, entry 1; cf. Table 1, entry 1 for reaction of **1d**). Thus the chloro substituent in **1d** is not required for good enantioselectivity or yield. The need for excess KHMDS in these reactions can be seen from comparing entries 1 and 2 and entries 4 and 5: when the amount of KHMDS is decreased from 2.5 to 1.2 equiv, very low consumption of starting material is observed and the yields of **17d** and **2d** decrease significantly.[25] A similar outcome is observed when HMPA is omitted from the reaction (cf. entries 1 and 3 and entries 4 and 6); we have previously reported the need to incorporate HMPA in alkylations of lithium enolates of 1,4-benzodiazepin-2-ones.[6]

***Table 2.*** Enantioselective Deprotonation/Alkylation Reactions of Ala-, Phe-, Abu-, and Met-Derived *N*-DAM-1,4-benzodiazepin-2-ones (*S*)-**5d**−**8d** at −42 °C




(*S*)-**5d**-**8d** **2d**, **17d**-**25d**

| entry | $R^1$ | $R^2$ | E[a] | product | HMPA (*n* equiv) | % yield | % ee[b] |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | Bn | (−)-**17d** | 6 | 78 | 98 *R*[c] |
| 2 | Me | H | Bn | (−)-**17d** | 6 | 11[d,e] | nd |
| 3 | Me | H | Bn | (−)-**17d** | 0 | 19[e] | nd |
| 4 | Bn | Cl | Me | (+)-**2d** | 6 | 79 | >99.5 *S* |
| 5 | Bn | Cl | Me | (+)-**2d** | 6 | 17[d,e] | nd |
| 6 | Bn | Cl | Me | (+)-**2d** | 0 | 23[e] | nd |
| 7 | Bn | Cl | allyl | (+)-**18d** | 6 | 58 | 92 |
| 8 | Bn | Cl | -CN | (+)-**19d** | 6 | 68 | 96 |
| 9 | Et | Cl | Bn | (−)-**20d** | 6 | 65 | 94 *R*[f] |
| 10 | Et | Cl | allyl[g] | (−)-**21d** | 6 | 58 | 94 |
| 11 | Et | Cl | -CN | (+)-**22d** | 6 | 86 | 96 |
| 12 | $MeSCH_2CH_2$- | Cl | Me | (−)-**23d** | 6 | 67 | 87 |
| 13 | $MeSCH_2CH_2$- | Cl | allyl | (−)-**24d** | 6 | 33 | 72 |
| 14 | $MeSCH_2CH_2$- | Cl | -CN | (−)-**25d** | 6 | 80 | 87 |

[a] Inverse addition of the enolate to the electrophile (equiv): MeI (10), BnBr (10), allyl bromide (10), tosyl cyanide (2.0). [b] Enantiomeric excess was measured by chiral stationary-phase HPLC; nd = not determined. Where indicated, absolute stereochemistry was determined by correlation; in all other cases, retentive substitution is assumed by analogy. [c] (*R*) Stereochemistry of (−)-**17d** was deduced on the basis of similar sign of rotation and HPLC elution order compared to chloro-substituted analogue (−)-**2d**. [d] Reaction with only 1.2 equiv KHMDS. [e] Reaction time was identical to that of entries 1 and 4 (1.5 h). [f] (*R*) Stereochemistry of (−)-**20d** was deduced on the basis of similar sign of rotation and HPLC elution order compared to Ala derivative (−)-**2d**. [g] Reaction was performed with allyl iodide, which proved superior to allyl bromide in this case.

The enolate generated from Phe-derived 1,4-benzodiazepin-2-one (*S*)-**6d** reacts at −42 °C in DME with methyl iodide, allyl bromide, and tosyl cyanide in moderate to good yields with excellent enantioselectivity (92−>99.5% ee; Table 2, entries 4, 7, and 8). Similarly good results are obtained for benzylation, allylation, and cyanation of the enolate generated from Abu-derived benzodiazepine (*S*)-**7d** (Table 2, entries 9−11). Finally, for reasons unknown, reactions of the Met-derivative (*S*)-**8d** proceed with somewhat lower enantioselectivity (72−87% ee; Table 2, entries 12−14).

A major criterion for selection of the DAM group was removability. The *N*-DAM group has been removed by oxidation,[12,14] reduction,[26] and acidic hydrolysis;[13] we chose the latter mode and realized excellent yields and selectivity (Table 3).

Particularly noteworthy is the deprotection of (−)-**10d** in 1.25% TFA in $CH_2Cl_2$ (1.5 h, room temperature), which provides the desired (−)-**10c** in quantitiative yield with no concurrent deprotection of the *N*-Boc group on the indole. Hydrolysis of *N*-H quaternary 1,4-benzodiazepin-2-ones (+)-**2c**, (+)-**9c**, and (−)-**12c** to the corresponding quaternary amino acids proceeds under milder conditions (6 M HCl, 125 °C, 2 days) than previously reported for hydrolysis of the *N*-*i*-Pr analogues. Quaternary amino acids (*R*)-(−)-α-Me-Phe-OH **26**,

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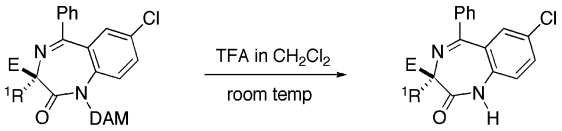
(24) The chloro substituent in these 1,4-benzodiazepin-2-ones derives from the 2-amino-5-chlorobenzophenone starting material, a commercially available intermediate used in the production of diazepam.
(25) One possible explanation for the need for excess base is that alkylation occurs more quickly on a KHMDS/potassium enolate mixed aggregate than it does on homomeric potassium enolates.
(26) Kobayashi, Y.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3041−3042.

***Table 3.*** Facile Acidic Removal of the *N*-DAM Group




**2d**, **9d-12d**, **20d** **2c**, **9c-12c**, **20c**

| entry | substrate | $R^1$ | E | % TFA–$CH_2Cl_2$ (v/v) | *t* (h) | % yield | % ee[a] |
|---|---|---|---|---|---|---|---|
| 1 | (−)-**2d** | Me | Bn | 25 | 1 | 96 | >99.5 *R* |
| 2 | (−)-**9d** | Me | 4-Me$C_6H_4CH_2$- | 6.25 | 1.5 | 98 | 99 *R* |
| 3 | (−)-**10d** | Me | *N*-Boc-indol-3-yl-$CH_2$- | 1.25 | 1.5 | 99 | >99.5 |
| 4 | (+)-**11d** | Me | allyl | 6.25 | 1.0 | 97 | 98 |
| 5 | (−)-**12d** | Me | $EtO_2CCH_2$- | 6.25 | 1.5 | 98 | 99 *R* |
| 6 | (−)-**20d** | Et | Bn | 25 | 0.75 | 94 | 98 *R* |
| 7 | (−)-**21d** | Et | allyl | 6.25 | 1.5 | 99 | 94 |

[a] Absolute stereochemistry was determined as listed in Tables 1 and 2.

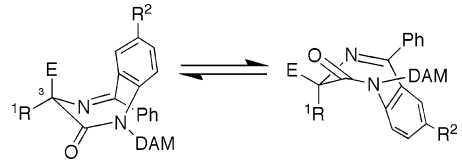
(*R*)-(−)-α-Me-4-Me-Phe-OH **27**, and (*R*)-(−)-α-Me-aspartic acid **28** were obtained in 72%, 76%, and 85% yield, respectively, confirming the absolute stereochemistry depicted in Table 1.

The conformational behavior of the quaternary *N*-DAM- and *N*-H-1,4-benzodiazepin-2-ones, as revealed by $^1$H NMR spectroscopy, is worthy of comment. Except for the 3-cyano derivatives, all the quaternary *N*-DAM-1,4-benzodiazepin-2-ones appear in $^1$H NMR spectra as mixtures of $R^1$-pseudoequatorial and $R^1$-pseudoaxial conformers in slow exchange; we have previously noted this behavior for quaternary *N*-Me, *N*-i-Pr, and *N*-PMB analogues.[6,11,27] Assignment of the individual conformers is straightforward, based on shielding of the pseudoaxial group by the benzo ring. Conformer ratios for the *N*-DAM-1,4-benzodiazepin-2-ones described in this work are listed in Table 4.

In most cases (entries 1−14), a near 50:50 mixture of conformers is seen, indicating similar steric demands of the $R^1$ and E substituents. In this context it may appear surprising that the corresponding *N*-H quaternary 1,4-benzodiazepin-2-ones (e.g., **2c**, **9c**−**12c**, and **20c**, Table 3) present only one set of resonances in their $^1$H NMR spectra. However, we attribute the spectral simplicity of these compounds to averaging caused by rapid interconversion between the diastereomeric conformers. This proposal is supported by the experimentally determined inversion barriers of glycine-derived benzodiazepines **29c** and **29e** (Scheme 3).

At room temperature, *N*-H-benzodiazepine **29c** presents a single, averaged resonance for the pseudoequatorial and pseudoaxial $CH_2$ protons in its $^1$H NMR spectrum, indicating rapid interconversion of the enantiomeric (*M*) and (*P*) conformers; decoalescence of these protons is observed at 253 K.[27,29] In contrast, *N*-benzhydrylbenzodiazepine **29e** displays discrete signals for the pseudoequatorial and pseudoaxial $CH_2$ protons, which do not coalesce until 458 K.[27] Returning to the *N*-DAM-3-cyano-substituted benzodiazepines **14d**, **19d**, **22d**, and **25d**, these appear as single, $R^1$-equatorial/CN-axial conformers by

***Table 4.*** Conformer Ratios for *N*-DAM-Substituted Quaternary 1,4-Benzodiazepin-2-ones

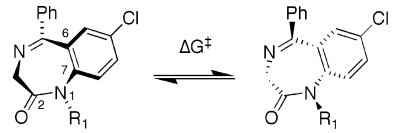



$R^1$-pseudoequatorial conformer $R^1$-pseudoaxial conformer

| entry | compd | $R^1$ | E | $R^2$ | mol % $R^1$ equatorial |
|---|---|---|---|---|---|
| 1 | **2d** | Me | Bn | Cl | 36 |
| 2 | **17d** | Me | Bn | H | 40 |
| 3 | **9d** | Me | 4-Me-$C_6H_4CH_2$- | Cl | 39 |
| 4 | **10d** | Me | *N*-Boc-indol-3-yl-$CH_2$- | Cl | 20 |
| 5 | **11d** | Me | allyl | Cl | 46 |
| 6 | **12d** | Me | $EtO_2CCH_2$- | Cl | 33 |
| 7 | **13d** | Me | Et | Cl | 50 |
| 8 | **16d** | Me | -N(Boc)NHBoc | Cl | nd[a] |
| 9 | **18d** | Bn | allyl | Cl | 65 |
| 10 | **20d** | Et | Bn | Cl | 30 |
| 11 | **21d** | Et | allyl | Cl | 40 |
| 12 | **23d** | $CH_3SCH_2CH_2$- | Me | Cl | 65 |
| 13 | **24d** | $CH_3SCH_2CH_2$- | allyl | Cl | 60 |
| 14 | **15d** | Me | $N_3$ | Cl | 70 |
| 15 | **14d** | Me | -CN | Cl | >99 |
| 16 | **19d** | Bn | -CN | Cl | >99 |
| 17 | **22d** | Et | -CN | Cl | >99 |
| 18 | **25d** | $CH_3SCH_2CH_2$- | -CN | Cl | >99 |

[a] nd, not determined due to overlapping resonances.

***Scheme 3.*** Barriers for Conformational Inversion in Glycine-Derived 1,4-Benzodiazepin-2-ones **29c** and **29e**[27] [a]




| | | ΔG‡ (kcal/mol) |
|---|---|---|
| (*M*)-**29c**: $R_1$ = H | (*P*)-**29c** | 12.3 |
| (*M*)-**29e**: $R_1$ = $CHPh_2$ | (*P*)-**29e** | 21.5 |

[a] (*M*) and (*P*) helical descriptors of configuration are assigned on the basis of the sign of the 2−1−7−6 dihedral angle.[28]

$^1$H NMR spectroscopy (Table 4, entries 15−18). Is this preference electronic or steric in nature? A strong preference for the CN-axial conformer in 2-cyanopiperidine has been attributed to the anomeric effect.[30] The anomeric effect may play some role in the conformational preference of **14d**, **19d**, **22d**, and **25d**, but we believe the strong preference for the CN-axial conformer in these compounds principally derives from the small size of the cyano group relative to that of $R^1$. For reference, the equatorial preferences for CN and methyl groups in a cyclohexane ring are 0.20 and 1.74 kcal/mol, respectively.[31]

To determine whether the DAM group would be effective for enantioselective deprotonation/alkylation of 1,4-benzodiazepine-2,5-diones, several substrates derived from proline, thioproline, *cis*-4-hydroxy-D-proline, and *trans*-4-hydroxy-L-proline were prepared (Scheme 4). *N*-H-1,4-Benzodiazepine-2,5-diones **3c**, **30c**, **31c**, and **32c** were prepared according to literature methods[32−34] by heating isatoic anhydride with the appropriate

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(28) This dihedral angle has the same sign as the C2−C3−N4−C5 dihedral, which has historically (Konowal, A.; Snatzke, G.; Alebic-Kolbah, T.; Kajfez, F.; Rendic, S.; Sunjic, V. *Biochem. Pharm.* **1979**, *28*, 3109−3113) been used to designate the sense of conformational chirality of the benzodiazepine ring.
(29) Linscheid, P.; Lehn, J.-M. *Bull. Chim. Soc. Fr.* **1967**, 992−997.
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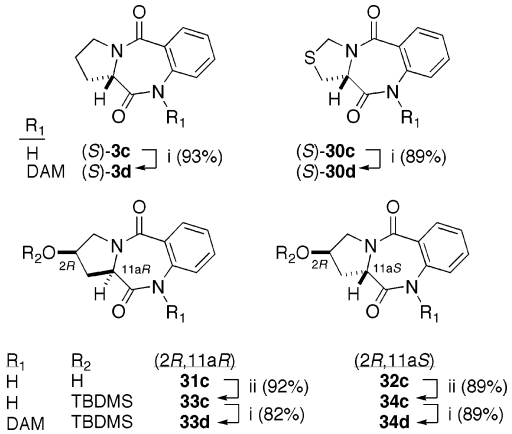
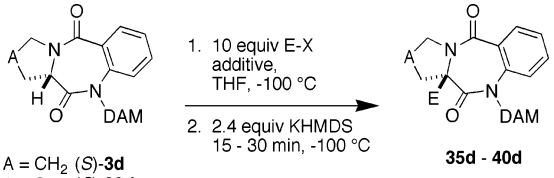
***Scheme 4.*** Synthesis of *N*-DAM-1,4-Benzodiazepin-2-ones Derived from (*S*)-Proline, (*S*)-Thioproline, *cis*-4-Hydroxy-D-proline, and *trans*-4-Hydroxy-L-proline[a]




[a] Reagents and conditions: (i) THF, NaH, 0 °C; DAM-Br. (ii) TBDMS-Cl, imidazole, DMF. Atom numbering is according to standard IUPAC pyrrolo[2,1-*c*][1,4]benzodiazepine convention.

***Table 5.*** Enantioselective Alkylation of *N*-DAM-1,4-Benzodiazepine-2,5-diones (*S*)-**3d** and (*S*)-**30d** Derived from Proline and Thioproline




| entry | A | E | additive | product | % yield | % ee[a] |
|---|---|---|---|---|---|---|
| 1 | $CH_2$ | Bn | HMPA[b] | (+)-**35d** | 98 | 98 *R* |
| 2 | $CH_2$ | Bn | HMPA[b] | (±)-**35d** | 90 | 0 (−78 °C)[c] |
| 3 | $CH_2$ | Bn | na | (+)-**35d** | 83 | 99 *R* |
| 4 | $CH_2$ | 4-Me-$C_6H_4CH_2$- | HMPA[b] | (+)-**36d** | 93 | >99.5 *R*[d] |
| 5 | $CH_2$ | 4-Me-$C_6H_4CH_2$- | na | (+)-**36d** | 83 | 99 *R*[d] |
| 6 | $CH_2$ | 2-Ph-$C_6H_4CH_2$- | HMPA[b] | (+)-**37d** | 94 | 99 *R*[d] |
| 7 | $CH_2$ | 2-Ph-$C_6H_4CH_2$- | na | (+)-**37d** | 87 | 94 *R*[d] |
| 8 | $CH_2$ | allyl | HMPA[b] | (+)-**38d** | 65 | 93 |
| 9 | $CH_2$ | allyl | na | (+)-**38d** | 90 | 92 |
| 10 | S | Bn | na | (+)-**39d** | 98 | 99 |
| 11 | S | allyl | na | (+)-**40d** | 89 | 95 |

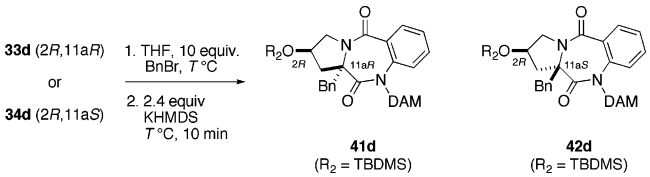
[a] Enantiomeric excess measured by HPLC. Where indicated, absolute stereochemistry was determined by correlation; in all other cases, retentive substitution is assumed. [b] Six equivalents of HMPA was added. [c] Reaction was carried out at −78 °C. [d] (*R*) Stereochemistry was assigned on the basis of polarimetry and HPLC elution order relative to the simple benzyl analogue.

proline derivative. Installation of the DAM group proceeded in excellent yield; in the case of **31c** and **32c**, protection of the hydroxyl group was carried out prior to N1-functionalization.

On the basis of our previous studies with *N*-*i*-Pr analogue (*S*)-**3a**,[7] we anticipated the need for cryogenic reaction temperatures and an in situ protocol to prevent racemization of the enolate derived from (*S*)-**3d**. In the presence of 10 equiv of benzyl bromide at −100 °C, (*S*)-**3d** reacts with KHMDS to give the desired benzylated product (+)-**35d** in 98% yield and 98% ee (Table 5, entry 1).

Interestingly, when the identical reaction is performed at −78 °C, racemic product is obtained, indicating that racemization of the enolate is faster than intermolecular alkylation at this higher temperature. This −100 °C protocol was then applied to other alkylations of (*S*)-**3d** and thioproline-derived (*S*)-**30d**. In all cases, excellent yields and enantioselectivities were obtained (Table 5, entries 3−11). It is important to note that addition of HMPA is not necessary to achieve high yields of the alkylated products from **3d** and **30d** (Table 5, cf. entries 1 and 3, 4 and 5, 6 and 7, and 8 and 9); in contrast, HMPA is required for acceptable yields in deprotonation/alkylation of 1,4-benzodiazepin-2-ones (cf. Tables 1 and 2). All the quaternary 1,4-benzodiazepine-2,5-diones derived from proline and thioproline appear as single conformers by $^1$H NMR spectroscopy. We attribute this conformational homogeneity to an amide resonance-imposed requirement for the proline moiety to occupy a pseudoequatorial orientation on the benzodiazepine ring.[7] Removal of the DAM group from (+)-**35d**, (+)-**37d**, and (+)-**38d** by treatment with 25% TFA in $CH_2Cl_2$ is complete within 3 h at room temperature, affording *N*-H analogues (+)-**35c**, (−)-**37c**, and (+)-**38c** in 99%, 99%, and 98% yields, respectively. Retentive transformation of (*S*)-(+)-**3d** to (*R*)-(+)-**35d** was proven by hydrolysis of (+)-**35c** to (*R*)-(−)-α-benzylproline.[35]

***Table 6.*** Deprotonation/Benzylation Reactions of Diastereomeric Substrates **33d** and **34d** Evidence Conformational Memory at −100 °C but Not at −78 °C




| entry | starting material | *T* (°C) | % yield (**41d** + **42d**) | ratio **41d**:**42d**[a] |
|---|---|---|---|---|
| 1 | **33d** | −100 | 95 | 96:4 |
| 2 | **34d** | −100 | 49 | 8:92 |
| 3 | **33d** | −78 | 87 | 69:31 |
| 4 | **34d** | −78 | 82 | 66:34 |

[a] Diastereomer ratios measured by chiral stationary-phase HPLC and confirmed by $^1$H NMR.

Similarly, **34d** gave an 8:92 ratio of **41d** and **42d**, again favoring the retentive product (Table 6, entry 2). Interestingly, the diastereomeric substrates **33d** and **34d** derived from *cis*-4-hydroxy-D-proline and *trans*-4-hydroxy-L-proline feature identical (*R*) configuration at the oxygen-bearing stereocenter C2 (pyrrolo[2,1-*c*][1,4]benzodiazepine numbering) but opposite configuration at the enolizable carbon C11a. As such, these substrates can provide another test for the presence or absence of conformational memory effects in the derived enolates; a similar strategy has been used to illustrate the importance of conformational chirality in alkylations of amino acid ester enolates.[36,37] The demonstrated preference for retentive substitution of 1,4-benzodiazepine-2,5-diones leads to the prediction that deprotonation/alkylation of **33d** would give **41d**, whereas **34d** would give **42d**. However, in the absence of conformational memory effects both substrates would produce the same enolate (or mixture of enolates), and thus give the same ratio of products **41d** and **42d**. In the event, deprotonation/benzylation of **33d** at −100 °C gave a 96:4 ratio of **41d**:**42d**, as expected, favoring the retentive product (Table 6, entry 1).

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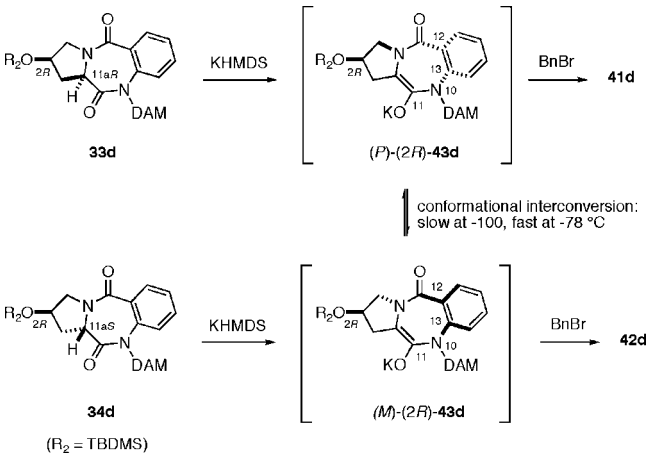
(37) Kawabata, T.; Chen, J.; Suzuki, H.; Fuji, K. *Synthesis* **2005**, 1368−1377.

***Scheme 5.*** Proposed Formation of Enolate Conformational Diastereomers from **33d** and **34d**[a]




[a] (*M*) and (*P*) helical descriptors of configuration are assigned on the basis of the sign of the 11−10−13−12 dihedral angle (IUPAC pyrrolo[2,1-*c*][1,4]benzodiazepine numbering).

when the same reactions were carried out at −78 °C, **33d** and **34d** gave similar product ratios, near 2:1 in favor of **41d** (Table 6, entries 3 and 4). To rationalize these divergent results, the simplest explanation is that the deprotonations of **33d** and **34d** give conformationally diastereomeric enolates. On the basis of the stereoelectronic requirements for deprotonation, and calculations on the *N*-*i*-Pr analogue (*S*)-**3a**,[7] we propose that deprotonation of (11a*R*)-configured **33d** gives an enolate in the (*P*) conformation, and deprotonation of (11a*S*)-configured **34d** gives an enolate in the (*M*) conformation (Scheme 5).

At −100 °C, conformational interconversion of (*P*)-(2*R*)-**43d** and (*M*)-(2*R*)-**43d** is slow relative to intermolecular alkylation, and thus retentive substitution predominates (Table 6, entries 1 and 2). However, at −78 °C, conformational interconversion is fast relative to intermolecular alkylation. The similar **41d**:**42d** ratios obtained from **33d** and **34d** under these conditions suggest that alkylation is occurring on a nearly equilibrated mixture of the (*M*) and (*P*) conformers of (2*R*)-**43d**. We similarly attribute the formation of the minor product diastereomers at −100 °C to a small amount of stereochemical leakage (i.e., (*M*)−(*P*) conformational interconversion).

In conclusion, use of the DAM group at N1 of 1,4-benzodiazepin-2-ones and proline-derived 1,4-benzodiazepine-2,5-diones allows construction of quaternary stereogenic centers in high enantioselectivity via deprotonation/alkylation. The large steric bulk of the DAM group imparts a significant barrier to racemization of the conformationally chiral enolate intermediates, allowing reactions of *N*-DAM-1,4-benzodiazepin-2-ones to be carried out at temperatures as high as −42 °C. In contrast, deprotonation/alkylation reactions of proline-derived *N*-DAM-1,4-benzodiazepine-2,5-diones must be carried out at −100 °C, apparently due to a lower racemization barrier of the derived enolates.[38] Following this retentive substitution process, the DAM group is easily removed by acidic hydrolysis, thereby allowing the subsequent installation of diverse N1 functionality.

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**Supporting Information Available:** Experimental procedures, characterization data, $^1$H NMR spectra, and complete refs 1 and 22. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0640142

(38) Consistent with this analysis, preliminary deprotonation/trapping studies of *N*-*i*-Pr-1,4-benzodiazepin-2-one (*S*)-**1d** indicate the potassium enolate has a racemization barrier of 18 kcal/mol (258 K). In contrast, the same technique indicates only a 12.5 kcal/mol barrier (173 K) for the potassium enolate derived from *N*-*i*-Pr-1,4-benzodiazepine-2,5-dione (*S*)-**3d** (P. C.-H. Lam, S. L. MacQuarrie-Hunter, and P. R. Carlier, unpublished work).