Letter

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Enantioselective Route to 5-Methyl- and 5,7-Dimethyl-6,7-dihydro-5H-dibenz[c,e]azepine: Secondary Amines with Switchable Axial Chirality

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ABSTRACT

(−)-5-Methyl-6,7-dihydro-5H-dibenz[c,e]azepine 4, a new secondary amine featuring an axis-center stereochemical relay, was prepared enantioselectively from 2′-acetylbiphenyl-2-carboxylic acid, using (R)-2-phenylglycinol as an auxiliary for the control of both elements of chirality. The biaryl axis in 4 preferentially adopts the aS-configuration, with the methyl substituent pseudoequatorial, but conversion into the corresponding N-Boc derivative locks the axis into the aR-configuration, as predicted on the basis of molecular mechanics calculations.

The conformational properties of a three-atom bridged biaryl of the form 1 equip such a unit with the axis-center stereochemical relay that is the key structural component in many catalytic enantioselective processes. This relay is exemplified by the metal-coordinated BINAP 2, in which the spatial arrangement of the diphenylphosphine groups in the region of the metal atom depends on the configuration of the biaryl axis.1 The same type of axis-center relay is present in colchicine 3, and its operation has an important bearing on the ability of this alkaloid and its analogues to bind to tubulin and thereby act as cytotoxic agents.2

Our interest in the mechanics and reversibility of this type of stereochemical relay led us to select 5-methyl-6,7-dihydro-5H-dibenz[c,e]azepine 4, the simplest axis-center combination, for a detailed study. Simple models of 4 demonstrate the mechanics of the coupling between the configurations of C(5) and the biaryl axis and show that the pseudoequatorial orientation of a 5R-substituent in the azepine ring demands an S-configured biaryl axis and vice versa (Scheme 1). By analogy with colchicine 3, it might be anticipated that the amine (5R)-4 would exist predominantly in the aS-configuration, although this type of equilibrium can be finely balanced.2a,3

Derivatives 5 of 6,7-dihydro-5H-dibenz[c,e]azepine have become prominent in applications of conformationally flex-


(5) Sutherland, I. O.; Ramsay, M. V. J. Tetrahedron 1965, 21, 3401.


(9) It is reported (Chem. Abstr. 1988, 108, 625) that the amine (±)-4 was prepared, together with several homologues, in the course of a study into the control of hyperlipidemia: Hall, I. H.; Wyrick, S. D.; Chapman, J. M. U.S. 4689326, 1987. However, the preparative procedure and the NMR data provided in this publication indicate that the compounds prepared were the symmetrical N-alkyl isomers.

Our route to (5R)-4 begins with the condensation of the bifenylenecarboxylic acid 11, prepared from diphenic anhydride in two steps by slight modifications of the published procedures,13 with (R)-2-phenylglycinol 12 under the conditions developed by ourselves14 and, independently, Levacher’s group,15 which provides the oxazolidine lactam 13 diastereoselectively and in good yield (Scheme 2). Lactams such as these are remarkably resistant to the formation of acyliminiums,14b and 13 proved stable to various reduction protocols that would normally involve such intermediates (Et3SiH/TFA, etc.). However, lactams are susceptible to hydroborating agents, and treating 13 with borane-methyl sulfide gave a mixture of two reduction products that were identified from spectroscopic data as the isomeric amines 15 and 16. It seemed likely that carbonyl and oxazolidine reduction had proceeded sequentially but that the stereoselectivity of the second reduction step was poor. This was remedied by reference to the pioneering work of the Meyers group, who observed that alanine often provided high diastereoselectivity in this type of reduction.17 Accordingly, the treatment of 13 with 4.7 equiv of alane gave a high yield of one of the two amines observed previously, and this was

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Scheme 1. Conformational Equilibrium in 5-Methyl-6,7-dihydro-5H-diben[c,e]azepine 4
characterized as the expected retention product 15 by X-ray crystallographic analysis of the derived quaternary ammonium salt 17, mp 156–157 °C (MeOH). Reductive cleavage of the chiral auxiliary from 15 via catalytic hydrogenation cleanly provided the target amine (–)-4 (94%) as a pale yellow oil, [α]D20 −23.5 ± 1 (c 0.65, CHCl3), δH (500 MHz, CDCl3) 1.50 (3 H, d, J = 6.6 Hz, 5-Me).

With the amine 4 in hand, we sought to introduce a second methyl group at C(7) and thereby gain access to the 5,7-dimethyl series that includes Kündig’s amine 8. The lithiation-based methodology developed for the α-alkylation of nitrogen heterocycles18 holds out the prospect of diastereoselectivity, and conversion of the fixed-axis dinaphthazepine 6 into the trans-5,7-dimethyl analogue 7 can be achieved through the use of amidine or nitroso activation.8 However, it was not known how a flexible biaryl such as 4 might respond to these protocols, and neither of them is particularly convenient. In the event, treating the Boc derivative 18, prepared from 4 in the usual way, with 6 equiv of sec-butyllithium at −78 °C, followed by iodomethane, gave a mixture of products dominated by the trans-dimethyl system contained a significant quantity of the gem-dimethyl isomer 20 [δH (500 MHz, CDCl3) 1.65 (6 H, br s, 2 × 5-Me), 1.51 (9 H, s, CMe3)], and on the basis of limited data it is speculated that only a small amount of the meso-diastereoisomer 21 [δH (300 MHz, CDCl3) 4.90 (1 H, q, J = 7.0 Hz, 5-H or 7-H), 1.38 (3 H, d, J = 7.0 Hz, 5-Me or 7-Me)] was among the reaction products. Several attempts to optimize the yield of 19 were thwarted by poor conversion which we attributed to aggregation phenomena, but the use of Schlosser’s “LIDAKOR” base19 provided 19 in 87% yield after chromatography. The removal of the Boc group from 19 using aqueous phosphoric acid20 gave the amine (–)-8, [α]D20 −81 ± 4 (c 0.61, CH2Cl2) [lit.10 [α]D20 −83.1 (0.61, CH2Cl2)].

The properties of the intermediates prepared en route to 4 and 8, when compared to those of the amines themselves, offer further insight into the mechanics and potential of the axis-center stereochemical relay in 6,7-dihydro-5H-dibenzo[c,e]azepines. The conformation of the seven-membered ring can generally be deduced via 1H NMR spectroscopy, a pseudoeaxial methyl group at C(5) or C(7) experiencing a marked upfield shift due to the effects of the distal aromatic ring.8,10,21 On this basis it can be seen that the conversion of the amine (–)-4 (δMe 1.50 ppm) into the Boc derivative (+)-18 (δMe 0.86 ppm) is accompanied by a change in the orientation of the methyl group from pseudoquartorial to 2009 1665

\[ \text{Scheme 2. Enantioselective Route to 4 from the Lactam 13' } \]

\[ \text{Scheme 3. Diastereoselective Methylation of 4 To Obtain 8 } \]

pseudoaxial. The mechanics of the axis-center relay (Scheme 1) require that this change be accompanied by the inversion of the biaryl axis, as can be inferred from the change in sign of the specific rotation,\(^{(22)}\) so it is demonstrated that the axial configuration of a 5-substituted amine such as 4 can be “switched” by modification of the nitrogen substituent. The preference of 18 for the (aR)-configuration is a natural consequence of the steric interaction between the 5-methyl and Boc groups, which is accentuated by the trigonalization of the nitrogen atom and mirrors the behavior of other Boc and Boc groups, which is accentuated by the trigonalization of the nitrogen atom and mirrors the behavior of other Boc-substituted nitrogen heterocycles.\(^{(18)}\) To gain a more quantitative view of this phenomenon, various alkyl-substituted 6,7-dihydro-5H-dibenzo[c,e]azepine derivatives were modeled using molecular mechanics techniques (Table 1).

**Table 1.** Calculated Differences in Steric Energy (kJ mol\(^{-1}\)) of the aS and aR Conformational Minima of Various 6,7-Dihydro-5H-dibenzo[c,e]azepine Derivatives (Macromodel 8.0, MM3)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>∆E&quot;</th>
<th>ratio²</th>
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<td>4</td>
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<td>H</td>
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<td>Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>3.7</td>
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<tr>
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<td>Pr</td>
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<td>H</td>
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<td>-37.9</td>
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</table>

-²Calculated difference in steric energy \(E_{aS} - E_{aR}\) (kJ mol\(^{-1}\)) of the respective global conformational minima in the aR and aS manifolds. The ratio aS:aR at 298 K assuming assuming equilibrium.

The modeling results are consistent with the observed preference of (5R)-4 and (5R,7R)-8 for the aS-configuration but suggest that N-acylation\(^{(23)}\) will invert and effectively “lock” the biaryl axis of this type of amine. The preference of the 5-alkyl substituent for a pseudoequatorial orientation decreases as its steric bulk increases and its interaction with H(4) becomes more significant, with the isopropyl system 23 being close to the crossover point. The proposal, made by Kündig et al.,\(^{(10)}\) that substitution at H(4) and H(8) of 8 should increase the preference of the 5- and 7-methyl groups for pseudoaxial orientations and thereby exaggerate the C₂-symmetric environment around the nitrogen atom is supported by the results for 25 and 26, suggesting that the lithium amides derived from these amines may be more effective than 8 as mediators of enantioselective deprotonation. Finally, the detailed mechanism of the trans-selective methylation of 18 to give 19 is unclear, but from the overwhelming preference of the model carbamate 31 for the aR-configuration, it can be inferred that, for the substrate 18, the pro-R location of C(7) will be pseudoaxial and therefore the more exposed, kinetically reactive site throughout the reaction sequence.

In conclusion, we have prepared (R)-5-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine (→-4, the first of a new series of secondary amines incorporating an axis-center stereocchemical relay, from 2′-acetylbiaryl-2-carboxylic acid using an auxiliary strategy for the simultaneous control of both elements of chirality. The amine (→-4 can be stereoselectively methylated to obtain the known (R,R)-5,7-dimethyl homologue (→-8 in three steps. The stereochemical relay in the amine 4 effectively extends to the nitrogen atom, where acylation has the effect of forcing the 5-methyl substituent into a pseudoaxial orientation, thereby inverting and locking the configuration of the biaryl axis. The mechanics of this type of relay may be useful for controlling the stereochemistry of functionalized biaryls, notably those with 2-arylpyridine or 2,2′-bipyridyl cores, as a component of molecular devices. We also anticipate that other types of bonding or coordination at nitrogen will elicit a quantifiable response in amines with this relay, which may therefore have analytical applications. These various possibilities are currently under investigation.

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**Supporting Information Available:** Experimental procedures and characterization of compounds, X-ray data, \(^1H\) and \(^13C\) NMR spectra, and structures generated via molecular mechanics calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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\(^{(23)}\) The \(^1H\) NMR chemical shift of the 5-methyl substituent in the tertiary amine 15 (δ₉ 0.92) is consistent with a pseudoaxial orientation, and therefore an aR-configuration for this compound, indicating that the conformation of the amine 4 can also be modified by N-alkylation.