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

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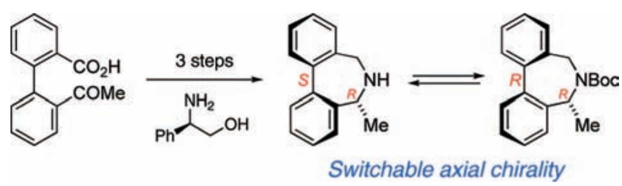
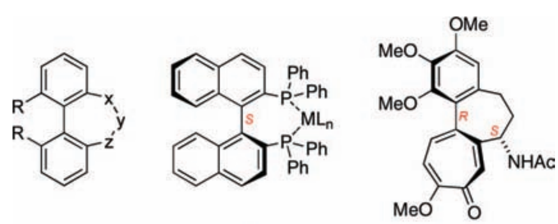
ABSTRACT



(−)-5-Methyl-6,7-dihydro-5*H*-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 a*S*-configuration, with the methyl substituent pseudoequatorial, but conversion into the corresponding *N*-Boc derivative locks the axis into the a*R*-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-5*H*-dibenz[*c*,*e*]azepine **4**, the simplest axis-center combination, for a detailed study. Simple models of **4** demonstrate



1 2 3

the mechanics of the coupling between the configurations of C(5) and the biaryl axis and show that the pseudoequatorial orientation of a 5*R*-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 (5*R*)-**4** would exist predominantly in the a*S*-configuration, although this type of equilibrium can be finely balanced.[2a,3]

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

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(1) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
(2) (a) Brossi, A. *J. Med. Chem.* **1990**, *33*, 2311. (b) For a correction, see: Berg, U.; Bladh, H. *Helv. Chim. Acta* **1999**, *82*, 323.

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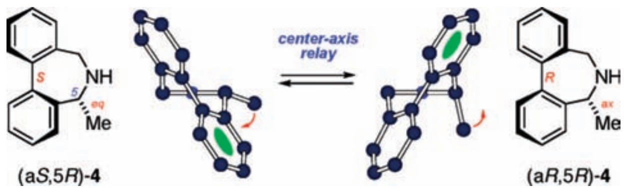
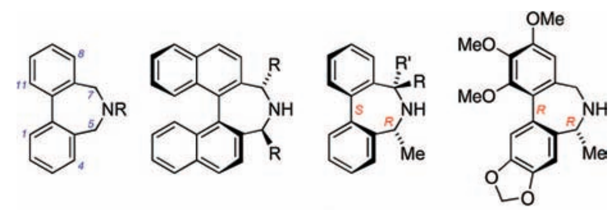
Scheme 1. Conformational Equilibrium in 5-Methyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine **4**



ible (*tropos*) biaryl units in various structural roles.[4] There is a relatively low barrier to axis inversion in such units (a value for $\Delta G^{\ddagger}$ of 56 kJ/mol for the inversion barrier in the *N*,*N*-dimethylammonium bromide was estimated from NMR data[5]), and the axial configuration is sensitive to central chirality in the R-group.[6] Studies into the use of homochiral amines as reagents, catalysts, and ligands have also featured fixed-axis dinaphthazepines such as **6**[7] and **7**.[8] In contrast, 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines bearing substituents at C(5) and/or C(7) are surprisingly rare, and the monoalkylated series that starts with **4** is unknown.[9] However, the dimethyl homologues **8** and **9** have been prepared by Kündig and co-workers,[10] who identified the lithium amide derived from **8** as an enantioselective base with some promise,[11] while more recently the preparation of the highly oxygenated derivative **10** was described by Baudoin and co-workers.[12] The published routes to **8** and **10** both involve the late formation of the Ar−Ar bond using Pd-catalyzed triflate-stannane (Stille)[10] or halide-boronate (Suzuki−Miyaura)[12] coupling protocols, respectively. We herein provide the details of an alternative approach to such compounds in which the axis-center stereochemical relay in the three-atom bridged biaryl is exploited at the outset, using a chiral auxiliary strategy, and in subsequent steps so as to provide (5*R*)-**4** and (5*R*,7*R*)-**8** in a concise and stereocontrolled sequence.



5 **6** R = H **7** R = Me **8** R = Me, R' = H **9** R = H, R' = Me **10**

Our route to (5*R*)-**4** begins with the condensation of the biphenylcarboxylic 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 ourselves[14] and, independently, Levacher's group,[15] which provides the oxazolidine lactam **13**[15] 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 (Et_3SiH/TFA, etc.). However, lactams are susceptible to hydroborating agents,[16] 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 alane 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

(3) (a) Brossi, A.; Boyé, O.; Muzaffar, A.; Yeh, H. J. C.; Toome, V.; Wegrzynski, B.; George, C. *FEBS Lett.* **1990**, *262*, 5. (b) For a pertinent discussion, see: Cavazza, M.; Zandomeneghi, M.; Pietra, F. *Tetrahedron Lett.* **2000**, *41*, 9129.

(4) For discussions and examples, see: (a) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561. (b) Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 6929. (c) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551. (d) Vial, L.; Lacour, J. *Org. Lett.* **2002**, *4*, 3939. (e) Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258. (f) Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369. (g) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (h) Scafato, P.; Cunsolo, G.; Labano, S.; Rosini, C. *Tetrahedron* **2004**, *60*, 8801. (i) Vachon, J.; Lauper, C.; Ditrich, K.; Lacour, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2334. (j) Aillaud, I.; Wright, K.; Collin, J.; Schulz, E.; Mazaleyrat, J.-P. *Tetrahedron: Asymmetry* **2008**, *19*, 82.

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

(6) (a) Superchi, S.; Bisaccia, R.; Casarini, D.; Laurita, A.; Rosini, C. *J. Am. Chem. Soc.* **2006**, *128*, 6893. (b) Dutot, L.; Wright, K.; Wakselman, M.; Mazaleyrat, J.-P.; Peggion, C.; De Zotti, M.; Formaggio, F.; Toniolo, C. *Tetrahedron Lett.* **2008**, *49*, 3475. (c) See also: Tichy, M.; Gunterova, J.; Zavada, J. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1080.

(7) For examples and leading references, see: (a) Maigrot, N.; Mazaleyrat, J.-P.; Welvart, Z. *J. Org. Chem.* **1985**, *50*, 3916. (b) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1992**, *57*, 2114. (c) Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2971. (d) Mazaleyrat, J.-P. *Tetrahedron: Asymmetry* **1997**, *8*, 2709. (e) Widhalm, M.; Nettekoven, U.; Mereiter, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4369. (f) Stranne, R.; Vasse, J.-L.; Moberg, C. *Org. Lett.* **2001**, *3*, 2525. (g) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (h) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Tetrahedron* **2006**, *62*, 11425. (i) Eberhardt, L.; Armspach, D.; Matt, D.; Toupet, L.; Oswald, B. *Eur. J. Org. Chem.* **2007**, 5395. (j) Shibatomi, K.; Tsuzuki, Y.; Nakata, S.; Sumikawa, Y.; Iwasa, S. *Synlett* **2007**, 551. (k) Vishnumaya; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117. (l) Zalubovskis, R.; Bouet, A.; Fjellander, E.; Constant, S.; Linder, D.; Fischer, A.; Lacour, J.; Privalov, T.; Moberg, C. *J. Am. Chem. Soc.* **2008**, *130*, 1845. (m) Li, X.-J.; Zhang, G.-W.; Wang, L.; Hua, M.-Q.; Ma, J.-A. *Synlett* **2008**, 1255. (n) Mazaleyrat, J.-P.; Wright, K. *Tetrahedron Lett.* **2008**, *49*, 4537.

(8) (a) Meyers, A. I.; Nguyen, T. H. *Tetrahedron Lett.* **1995**, *36*, 5873. (b) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194. (c) Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073. (d) Pisani, L.; Superchi, S. *Tetrahedron: Asymmetry* **2008**, *19*, 1784.

(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.

(10) Saudan, L. A.; Bernardinelli, G.; Kündig, E. P. *Synlett* **2000**, 483.

(11) Pache, S.; Botuha, C.; Franz, R.; Kündig, E. P.; Einhorn, J. *Helv. Chim. Acta* **2000**, *83*, 2436.

(12) (a) Joncour, A.; Décor, A.; Thoret, S.; Chiaroni, A.; Baudoin, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 4149. (b) Joncour, A.; Décor, A.; Liu, J.-M.; Tran Huu Dau, M.-E.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 5450.

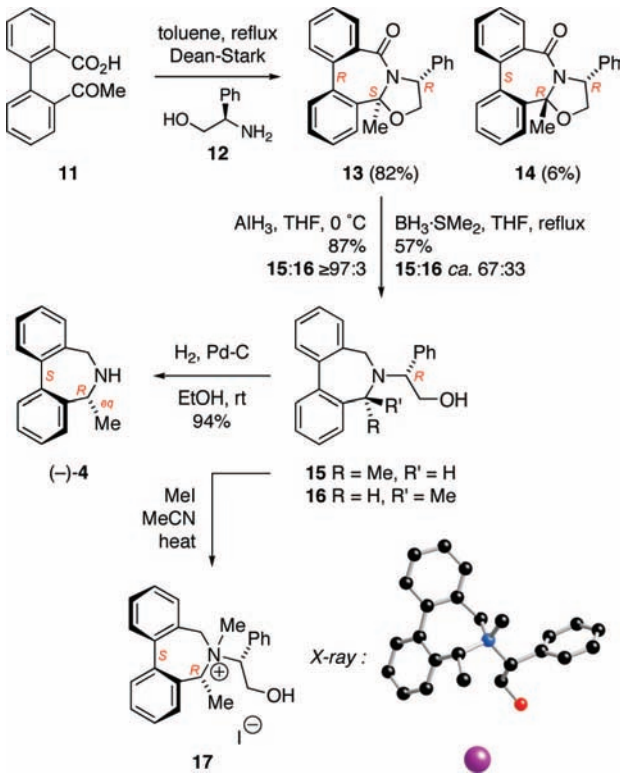
(13) Ried, W.; Conte, R. *Chem. Ber.* **1971**, *104*, 1573.

(14) (a) Edwards, D. J.; Pritchard, R. G.; Wallace, T. W. *Tetrahedron Lett.* **2003**, *44*, 4665. (b) Edwards, D. J.; House, D.; Sheldrake, H. M.; Stone, S. J.; Wallace, T. W. *Org. Biomol. Chem.* **2007**, *5*, 2658.

(15) Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517.

(16) (a) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912. (b) Brown, H. C.; Nazer, B.; Cha, J. S.; Sikorski, J. A. *J. Org. Chem.* **1986**, *51*, 5264. (c) Collins, C. J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 3673.

Scheme 2. Enantioselective Route to **4** from the Lactam **13**[a]

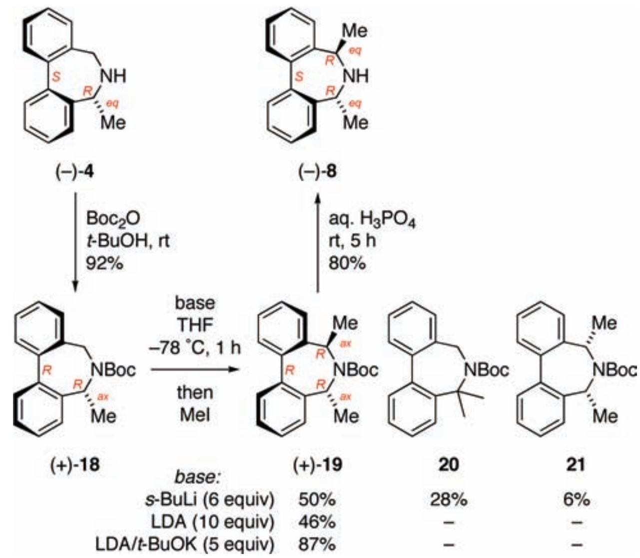


[a] For clarity, the hydrogen atoms are omitted from the X-ray crystal structure of the quaternary salt **17**.

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, $[\alpha]^{25}_{D}$ −23.5 ± 1 (*c* 0.65, $CHCl_3$), δ_H (500 MHz, $CDCl_3$) 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 heterocycles[18] 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 **19** [δ_H (500 MHz, $CDCl_3$) 1.54 (9 H, s, $OCMe_3$), 0.89 (6 H, d, *J* = 7.0 Hz, 5-Me)] (Scheme 3). The product mixture also

Scheme 3. Diastereoselective Methylation of **4** To Obtain **8**



contained a significant quantity of the *gem*-dimethyl isomer **20** [δ_H (500 MHz, $CDCl_3$) 1.65 (6 H, br s, 2 × 5-Me), 1.51 (9 H, s, CMe_3)], and on the basis of limited data it is speculated that only a small amount of the *meso*-diastereoisomer **21** [δ_H (300 MHz, $CDCl_3$) 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_{eq} or 7-Me_{eq})] 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" base[19] provided **19** in 87% yield after chromatography. The removal of the Boc group from **19** using aqueous phosphoric acid[20] gave the amine (−)-**8**, $[\alpha]^{25}_{D}$ −81 ± 4 (*c* 0.61, CH_2Cl_2) {lit.[10] $[\alpha]^{20}_{D}$ −83.1 (*c* 0.61, CH_2Cl_2)}.

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-5*H*-dibenz[*c*,*e*]azepines. The conformation of the seven-membered ring can generally be deduced via ^1H NMR spectroscopy, a pseudoaxial 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** (δ_{Me} 1.50 ppm) into the Boc derivative (+)-**18** (δ_{Me} 0.86 ppm) is accompanied by a change in the orientation of the methyl group from pseudoequatorial to

(17) (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656. (b) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413.

(18) (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (b) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652. (c) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552, and references cited therein.

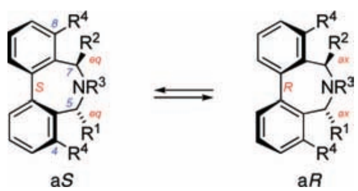
(19) Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *22*, 2401. (b) Takagishi, S.; Schlosser, M. *Synlett* **1991**, 119.

(20) Li, B.; Berliner, M.; Buzon, R.; Chiu, C. K.-F.; Colgan, S. T.; Kaneko, T.; Keene, N.; Kissel, W.; Le, T.; Leeman, K. R.; Marquez, B.; Morris, R.; Newell, L.; Wunderwald, S.; Witt, M.; Weaver, J.; Zhang, Z.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 9045.

(21) For examples in the analogous phosphepine series, see Kasák, P.; Mereiter, K.; Widhalm, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3416.

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 (a*R*)-configuration is a natural consequence of the steric interaction between the 5-methyl and Boc groups, which is accentuated by the trigonalisation 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-5*H*-dibenz[*c*,*e*]azepine derivatives were modeled using molecular mechanics techniques (Table 1).

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



	R^1	R^2	R^3	R^4	ΔE^a	ratio^b
4	Me	H	H	H	4.4	86:14
8	Me	Me	H	H	11.2	99:1
22	Et	H	H	H	3.7	82:18
23	Pr^i	H	H	H	0.5	55:45
24	Bu^t	H	H	H	−2.0	31:69
25	Me	H	Me	Me	−8.2	4:96
26	Me	Me	Me	Me	−14.9	0.2:99.8
27	Me	H	CHO	H	−11.4	1:99
28	Me	Me	CHO	H	−26.9	0:100
29	Me	H	COMe	H	−18.9	0:100
30	Me	Me	COMe	H	−38.6	0:100
31	Me	H	CO_2Me	H	−19.2	0:100
32	Me	Me	CO_2Me	H	−37.9	0:100

^{a} Calculated difference in steric energy $E_{aR} - E_{aS}$ (kJ mol^{-1}) of the respective global conformational minima in the a*R* and a*S* manifolds. ^{b} The ratio a*S*:a*R* at 298 K assuming dynamic equilibrium.

The modeling results are consistent with the observed preference of (5*R*)-**4** and (5*R*,7*R*)-**8** for the a*S*-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 C_2-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 a*R*-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-5*H*-dibenz[*c*,*e*]azepine (−)-**4**, the first of a new series of secondary amines incorporating an axis-center stereochemical relay, from 2′-acetylbiphenyl-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, or 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, ^{1}H and ^{13}C 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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(22) Fitts, D. D.; Siegel, M.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 480.

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

(24) Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.