Pergamon

Tetrahedron Letters 42 (2001) 9–12

TETRAHEDRON LETTERS

Asymmetric synthesis of 1-aryl 2,3,4,5-tetrahydro-2-benz[*c*]azepines

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Received 20 September 2000; revised 19 October 2000; accepted 23 October 2000

Abstract—The first stereoselective synthesis of 1-aryl-2-benz[*c*]azepines is described using oxazolidines as chiral inducers.

The synthesis of 1-phenyl tetrahydrobenzazepines is a topic of continuing interest since these types of compounds have been found to exhibit antihypertensive[1] **1**, anticonvulsant[2] **2** and antiarrhythmic[3] **3** activities. Furthermore, these compounds are useful for treatment of mental disorders and hypoxia[4] **4** (Fig. 1). Several synthetic strategies have been employed for the construction of racemic 1-aryl-2-benzazepine system based mainly on classical processes such as the Bischler Napieralski[5] and Pictet–Spengler[6] reactions or miscellaneous methods such as the intramolecular phenolic cyclization,[7] Meisenheimer rearrangement[8] and palladium catalyzed arylation.[9] The asymmetric synthesis of this system remains unexplored, however.

In the present work we describe the asymmetric synthesis of 1-aryl-2-benzazepines using an oxazolidine moiety as a chiral inducer. Oxazolidines have been widely exploited as chiral auxiliaries directed to the formation of a new stereogenic center.[10] Indeed, the particular addition of organometallic reagents to chiral oxazolidines has enjoyed widespread success in asymmetric synthesis.[11] In addition, oxazolidines can be easily prepared from aminoalcohols.[12]

The most practical route to the synthesis of aminoalcohols is the opening of epoxide rings with amines.

Usually, unsymmetrical epoxides undergo regioselective addition of the nucleophile to the less substituted carbon atom. In the case of styrene oxide, however, it is possible to obtain a reversal of the regiochemistry of the opening process.[13]

On the basis of the above information, we envisaged the preparation of two different chiral oxazolidines **10** and **11** (Scheme 1) from the two aminoalcohols **6** and **7**. We carried out the reaction of benzazepine **5** with (*R*)-(+)-styrene oxide under different conditions to afford isomeric mixtures of aminoalcohols **6** and **7**. The use of 1 equiv. of NaH in dry THF gave the aminoalcohol **6** as the major product (9:1) in 83% yield. Otherwise using 1 equiv. of $LiClO_4$ gave reversal ratio; in this case aminoalcohol **7** was the major product (9:1) in 81% yield. These compounds were separated by fractional crystallization.

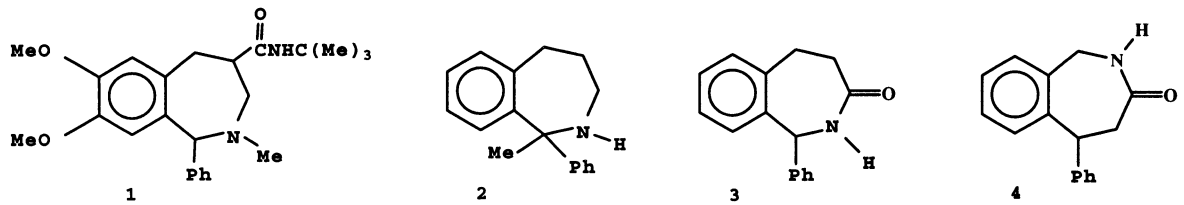

Figure 1.

Keywords: chirals 1-arylbenzazepines; 1,3-oxazolidines; aminoalcohols.

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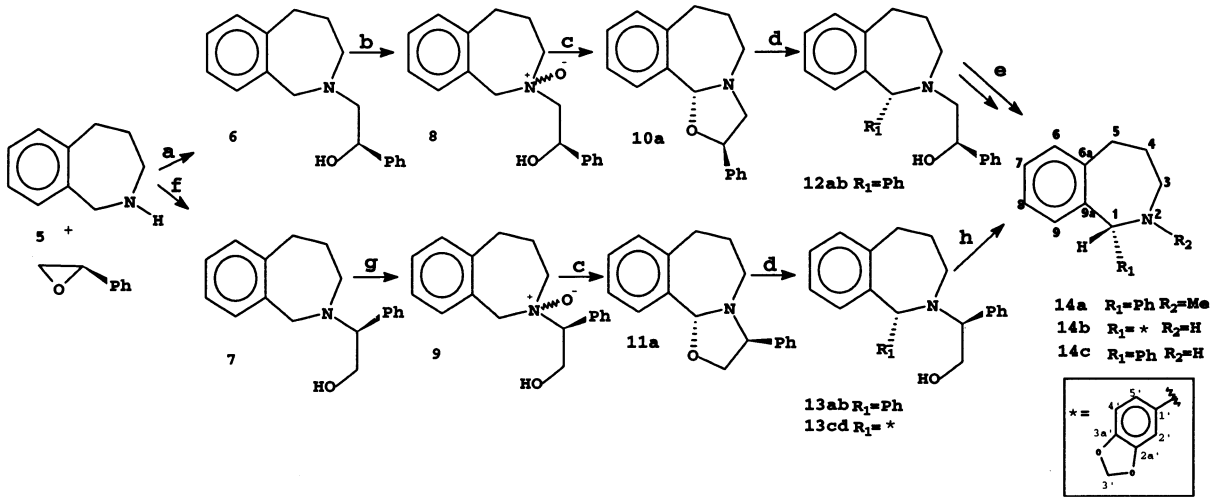
0040-4039/01/$ - see front matter
PII: S0040-4039(00)01881-5



Scheme 1. Reagents and conditions: (a) NaH, THF, 80°C; (b) H_2O_2 30%, MeOH, 10°C; (c) BuLi, THF, −78°C; (d) RMgBr, THF, −78°C; (e) MeI, CH_3CN. 60°C, *t*-BuOK/*t*-BuOH, 80°C; (f) CH_3CN, $LiClO_4$, 30°C; (g) H_2O_2 30%, MeOH, rt; (h) H_2 Pd/C.

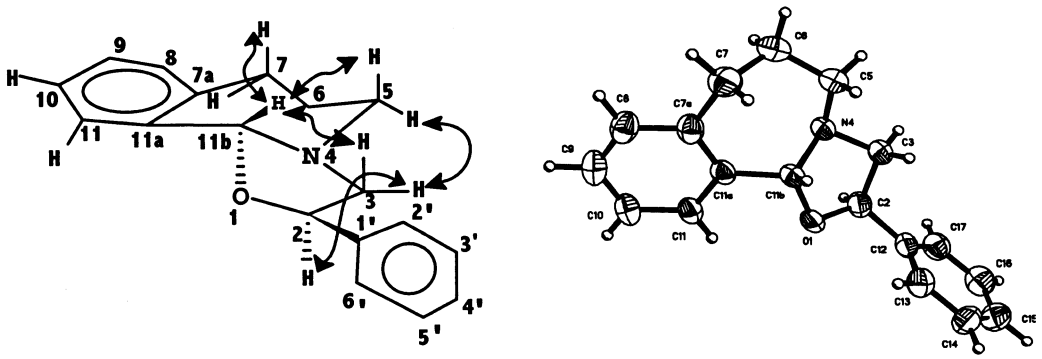
Compound **6** and **7** were transformed into the corresponding *N*-oxides **8** and **9** by treatment with hydrogen peroxide (5 equiv.) in 90% yield. These compounds were air and light sensitive and were used for the next reaction without further purification.[14]

N-Oxides **8** and **9** were treated with BuLi to afford pairs of the diastereomeric oxazolidines **10a/10b** (8:2) and **11a/11b** (95:05) in 51 and 58% yield, respectively.[15] The diastereomeric ratio and the absolute configuration of the major products **10a** and **11a** were determined by ^{1}H NMR and NOESY experimental analyses.[16] The β-orientation of H-11b for compound **10a** was ascertained by the observed dipolar interactions between this hydrogen with H-7β (δ 2.93), H-5β (δ 2.70) and H-3β (δ 2.67) (Fig. 2). The observed cross-peaks between H-3α (δ 3.63), H-2α (δ 5.30) and H-5α (δ 3.41) confirmed the assigned configuration at C-11b and established the extended conformation of the seven-membered ring. Furthermore, the configuration for **10a** was confirmed by X-ray analysis (Fig. 2). A similar analysis by NMR was made for compound **11a**.

The diastereoselective addition of Grignard reagents to chiral oxazolidines **10a** and **11a** gave the mixture of diastereoisomers **12a/12b**, **13a/13b** and **13c/13d** in a 8:2, 9:1 and 9:1 ratio in 58, 65 and 60% yield, respectively. The diastereomeric ratios of **12a/12b**, **13a/13b** and **13c/13d** were determined from the mixture by analyzing relevant signals in the ^{1}H NMR spectra.

NOESY experiments performed on **12a** indicated that the stereochemistry at C-1 remained unchanged due to the interactions between H-1 (δ 5.02), with H-9 (δ 6.96), and with the pro-*S* hydrogen at C-1′. The minor compound **12b** possesses the phenyl group attached at C-1 with a β-orientation, since H-9 is shielded (δ 6.81) in comparison with the major stereoisomer **12a**, where H-9 resonates at δ 6.96 and therefore the phenyl group is α-oriented (Fig. 3). A NOESY correlation between H-1α and H-2′ for **12b** confirmed the stereochemical assignments. Similar analyses by NMR were performed for compounds **13**.

The diastereoselectivity of this reaction can be rationalized by assuming that the Grignard reagent approaches the oxygen atom of the 1,3-oxazolidine ring to give a favorable intermediate immonium salt and nucleophilic attack occurs from the same face, in agreement with previous observations.[17]



10a 10a

Figure 2.

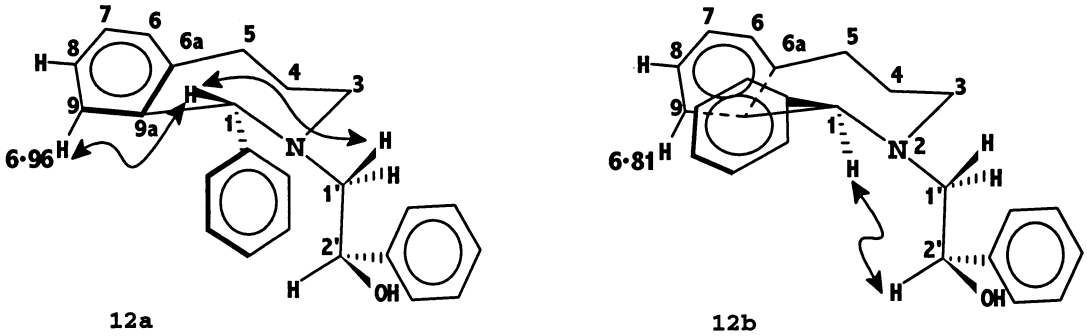


Figure 3.

A mixture of **12a/12b** (8:2) was converted into the *N*-methylammonium salt by treatment with methyl iodide in acetonitrile and reacted in situ with *t*-BuOK in *t*-BuOH to afford **14a** (8:2 ee) in 50% yield. Compounds **13a/13b** and **13c/13d** were treated under catalytic hydrogenation with Pd/C to afford the desired arylbenzazepine **14b** (9:1 ee) in 55% yield and **14c** (9:1ee) in 60% yield.[18]

In summary, 1,3-oxazolidines **10a** and **11a** are useful chiral inducers in the stereoselective synthesis to 1-aryl-2-benz[*c*]azepines. To the best of our knowledge, this procedure represents the first asymmetric synthesis for these kind of compounds.

Acknowledgements

Financial support from CONACYT is gratefully acknowledged. We also want to thank to A. Toscano, A. Peña, L. Velasco, R. Patiño, W. Matus, C. Márquez and J. Pérez for technical support.

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16. Spectral data of selected products: Compound **10a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.67 (td, $J = 12.0, 12.0, 3.0$ Hz, 1H, H-3β), 3.63 (dd, $J = 10.0, 5.0$ Hz, 1H, H-3α), 5.30 (dd, $J = 10.0, 5.0$ Hz, 1H, H-2α), 5.4 (s, 1H, H-11b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.10 (C-6), 34.59 (C-7), 56.40 (C-5), 64.44 (C-3), 78.37 (C-2), 95.31 (C-12), 123.77 (C-11), 126.13 (C-2′, C-6′), 126.44 (C-10), 127.69 (C-9), 127.89 (C-4′), 128.49 (C-3′, C-5′), 129.0 (C-8), 139.42 (C-7a), 140.39 (C-1′), 140.42 (C-11a); IR ($CHCl_3$): 1149.5, 1105.2, 1060.8 cm^{-1}; MS: E.I *m*/*z* (%) M$^+$ 265 (8.6), 264 (M−1), (50.3) 159 (100). Compound **11a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (dd, $J = 3.0, 3.5$ Hz, 2H, H-2β, H-3α), 4.31 (dd, $J = 3.0, 3.5$ Hz, 2α), 5.34 (s, 1H, H-11b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.22 (C-6), 34.85 (C-7), 54.37 (C-5), 70.24 (C-3), 73.30 (C-2), 95.45 (C-11b), 123.66 (C-11), 127.45 (C-10), 127.88 (C-4′), 127.96 (C-2′, C-6′), 128.49 (C-3′, C-5′), 129.02 (C-8), 129.23 (C-9), 138.15 (C-1′), 139.78 (C-8a), 140.99 (C-11a); IR ($CHCl_3$): 1199.7, 1175.0, 1122.5 cm^{-1}; MS: Fab *m*/*z* (%) M$^+$ 265 (34), 264 M−1 (100), 154 (65), 136 (42).
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18. Selected spectral data of final products: Compound **14a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70 (m, 2H, H-4), 2.41 (s, 3H, Me), 2.76 (ddd, $J = 14.0, 9.5, 3.5$ Hz, 2H, H-5α, H-5-β), 2.91 (ddd, $J = 8.4, 4.5, 3.4$ Hz, 1H, H-3β), 3.17 (ddd, $J = 10.7, 7.4, 3.0$ Hz, H-3α), 5.03 (s, 1H, H-1β), 7.0 (d, $J = 6.5$ Hz, 1H, H-9), 7.1–7.6 (m, 8H); IR: ($CHCl_3$) 2928.3, 2854.4, 1600.2 cm^{-1}; MS: E.I *m*/*z* (%) 237 M$^+$ (28.9), 160 (100). Compound **14b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.77 (m, 2H, H-4), 2.92 (ddd, 1H, H-5β), 3.12 (ddd, 1H, H-5α), 3.18 (ddd, 1H, H-3β), 3.37 (ddd, 1H, H-3α), 5.19 (s, 1H, H-1β), 6.61 (d, 1H, H-9), 7.0 (ddd, 1H, H-7), 7.18 (d, 1H, H-4′), 7.31 (d, $J = 7.0$, 2H, H-2′, H-6′), 7.36 (dd, $J = 7.0, 7.0$, 2H, H-3′, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.85 (C-4), 35.69 (C-5), 50.71 (C-3), 65.70 (C-1), 125.97 (C-8), 126.93 (C-7), 126.97 (C-4′),

127.87 (C-2′, C-6′), 127.97 (C-9), 128.44 (C-3′, C-5′), 129.72 (C-6), 132.56 (C-6a), 142.42 (C-9a), 142.42 (C-1′); IR ($CHCl_3$): 3445.8, 2933.6 cm^{-1}; MS: E.I m/z (%) 223 M^+ (30), 160 (100). Compound **14c**: ^1H NMR (500 MHz, CD_3OD): δ 1.84 (m, 2H, H-4), 2.67 (ddd, $J = 15.6$, 7.8, 7.8 Hz, 2H, H-5α, H-5β), 2.88 (ddd, $J = 15.6$, 7.8, 7.8 Hz, 2H, H-3α, H-3β), 3.94 (s, 1H, H-1), 5.86 (s, 2H, OCH_2O), 6.56 (s, 1H, H-5′), 6.57 (d, $J = 7.8$ Hz, 1H, H-2′), 6.70 (dd, $J = 7.5$, 1.0, 1H, H-3′), 7.08–7.21 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.62 (C-4), 30.39 (C-5), 39.34 (C-1), 40.51 (C-3), 102.14(C-4′), 109.10 (C-3′), 109.96 (C-5′), 122.5 (C-2′), 127.61 (C-8), 127.86 (C-7), 130.31 (C-6), 131.70 (C-9), 136.07 (C-9a), 139.97 (C-6a), 139.97 (C-1′), 147.29 (C-2a′), 149.23 (C-3a′); IR ($CHCl_3$): 2929.0, 2854.5 cm^{-1}; MS: C.I. m/z (%) 268 M+1 (100), 252 (72), 146 (21).