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Stereoselective synthesis of octahydro-3b*H*-[1,3]dioxolo[4″,5″:4′,5′]furo[2′,3′:5,6]pyrano[4,3-*b*]-quinolines via intramolecular hetero-Diels–Alder reactions catalyzed by bismuth(III) chloride†

Gowravaram Sabitha,[a,*] E. Venkata Reddy,[a] J. S. Yadav,[a] K. V. S. Rama Krishna[b] and A. Ravi Sankar[b]

[a]*Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*NMR Group, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

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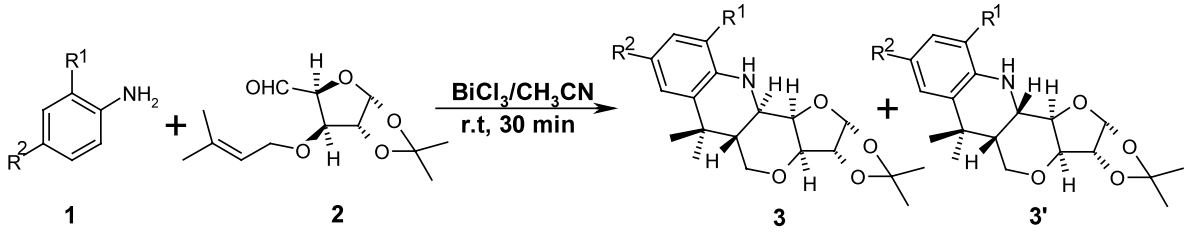
Abstract—A new, efficient and stereoselective synthesis of furo[2′,3′:5,6]pyrano[4,3-*b*]quinoline derivatives **3** and **3′** has been achieved by intramolecular hetero–Diels–Alder reactions of aldimines generated in situ from aromatic amines and the *O*-allyl derivative of the chiral sugar derived aldehyde **2** in acetonitrile in the presence of a catalytic amount of $BiCl_3$. The products are formed with extremely high *trans* selectivity in good to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

Intramolecular cycloaddition reactions with high regio- and stereocontrol are important tools for the efficient assembly of complex molecular structures.[1] This strategy has been successfully applied to the synthesis of tetrahydroquinoline derivatives in solution[2] as well as on solid phase.[3] These compounds are an important class of natural products and are endowed with a wide spectrum of interesting biological activities.[4] The high potential of these derivatives in a range of biological applications[5] makes them inviting targets for synthesis. Fused *O*-heterocycles, such as furano-pyrans, being constituents of bioactive compounds[6] are also targets for synthetic organic chemists. Recently we have initiated a program on the study of [4+2] cycloaddition reactions for the synthesis of tetrahydroquinoline derivatives.[7] This protocol involves the reaction of anilines with substrates containing an aldehyde moiety and an olefinic tether. Carbohydrates have been used as chiral auxiliaries or chiral building blocks[8] and used in asymmetric transformations due to their known absolute stereochemistry, ready availability and often their low cost. Recently bismuth(III) derivatives[9] have emerged as efficient catalysts in various organic transformations of interest because of their eco-friendly characteristics. In continuation of our interest in intramolecular hetero-Diels–Alder reactions,[7] we report herein $BiCl_3$-catalyzed highly efficient and stereoselective synthesis of 2,2,6,6-tetramethyl-3a,5,5a,6,11,11a,11b,12a-octahydro-3b*H*[1,3]dioxolo[4″,5″:4′,5′]furo-[2′,3′:5,6]pyrano[4,3-*b*] quinolines using [4+2] cyclo-



Scheme 1.

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* Corresponding author.
† IICT Communication No. 020211.

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addition reactions of anilines with the *O*-allyl derivative of the sugar derived aldehyde **2** from D-glucose (Scheme 1).

The reaction of aniline **1a** with the *O*-allyl derivative of the aldehyde **2**[10] in acetonitrile in the presence of 10 mol% $BiCl_3$ furnished a diastereomeric mixture of *trans* and *cis* products **3** and **3′**[11] in a 93:7 ratio in 81% yield. The reaction was very rapid and complete in 30 min, as indicated by TLC, and may proceed by in situ generation of the imine followed by an intramolecular [4+2] cycloaddition reaction to afford the products. Although it can be considered that the products result from a Diels–Alder reaction, a stepwise mechanism might actually be operating. The ratio of the products was determined by isolating the two isomers in pure form using silica gel column chromatography and the stereochemical structures were obtained from incisive NMR experiments. Interproton coupling constants and characteristic NOEs were used to obtain the proposed structures. These structures were further supported by minimum energy calculations.[12]

In the ^{1}H NMR spectrum of **3d**, vicinal coupling of 11.3 Hz for $J_{5a–5' (pro-R)}$ indicates a 1,2 diaxial disposition in a chair conformation. Also, the other coupling values such as $J_{5a–11a}=11.3$ Hz and $J_{11a–11b}=3.5$ Hz suggest that H_{11a} is on the opposite side of H_{5a}, with the *R* configuration at C-11a, which is further confirmed by the presence of 1,3 diaxial proximities like H_{11a}–H_{3b}, $H_{5' (pro-R)}$–H_{3b}, H_{11a}–$H_{5' (pro-R)}$ in the 2D NOESY spectrum. These observations show that the hexose ring adopts a $^{5a}C_{3b}$ chair conformation, which is also *trans* fused to the aza ring. Inter-ring NOEs like H_{5a}–Me-C, H_{11b}–Me-D and $H_{5' (pro-R)}$–Me-D support the assigned stereochemistry. NOEs between Me-A and H_{3a} and H_{12a} indicated that the isopropylidene group adopted the envelope conformation. Further, the energy-minimized structure is in agreement with the structure derived from the NMR data as shown in Fig. 1.

In compound **3′d**, a vicinal coupling value of about 11.6 Hz for H_{5a}–$H_{5' (pro-R)}$ indicates a 1,2-diaxial disposition in a chair conformation. In Fig. 2, NOE between H_{3b}–$H_{5' (pro-R)}$ indicates that they are on the same side in the hexose ring and the small coupling between $J_{11b–11a}$ (2.8 Hz) suggests that H_{11a} is *trans* to H_{11b}, with the *S* configuration at C-11a. Other couplings like $J_{5a–11a}=4.1$ Hz, $J_{5a–5' (pro-R)}=4.1$ Hz once again suggest a $^{5a}C_{3b}$ chair conformation for the hexose ring, which is *cis* fused to the aza ring. The energy-minimized structure, as shown in Fig. 2, is also in agreement with the stereo-assigned structure derived from NMR data.

Under similar conditions, several aromatic amines **1b–i** were treated with the *O*-allyl derivative **2** to illustrate the novelty of the present strategy and the results are presented in Table 1. In all cases the reactions are highly stereoselective, leading to the formation of *trans* isomers as the major products and *cis* isomers as minor products. When a bulky group such as *t*-butyl is present *ortho* to the amine (entry 3), only one diastereoisomer was isolated. Although Lewis acids such as $ZnCl_2$, $FeCl_3$, $ZrCl_4$, $AlCl_3$ and $BF_3{\cdot}OEt_2$ have been found to promote the intramolecular hetero-Diels–Alder reaction, more than stoichiometric amounts of acids were required with some decomposition. The reaction times were also too long with only moderate yields. On the other hand, $BiCl_3$-catalyzed reactions overcame the aforementioned drawbacks and are therefore more effective.

In conclusion, we have described a novel, highly efficient and stereoselective method for the synthesis of octahydro - 3b*H*[1,3]dioxolo[4″,5″:4′,5′]furo[2′,3′:5,6]-pyrano[4,3-*b*]quinoline derivatives of possible biological interest. This protocol relies on an intramolecular [4+2] cycloaddition reaction of an imine derived in situ from a sugar derived chiral template and aromatic amines. The synthesis of 'aza' and 'thia' analogs of these derivatives is under progress and the results will be published in due course.

Figure 1. Characteristic NOEs, minimum energy structure and chemical structure for **3d**.

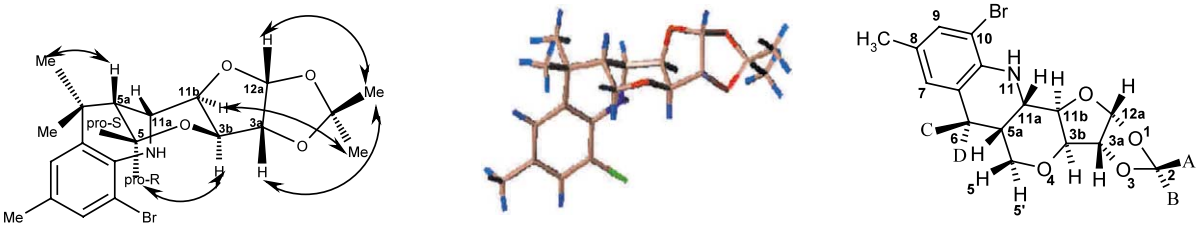

Figure 2. Characteristic NOEs, minimum energy structure and chemical structure for **3′d**.

Table 1. $BiCl_3$-catalyzed synthesis of octahydro-furo-pyranoquinolines[a,b]

Entry	Substrate (amine)	R^1	R^2	**3** and **3′**	
				Total yield[c] (%)	Ratio[d] *trans*:*cis*
1	**1a**	H	H	81	93:7
2	**1b**	CH_3	H	76	94:6
3	**1c**	*t*-Bu	H	71	100:0
4	**1d**	Br	CH_3	74	95:5
5	**1e**	H	Cl	76	96:4
6	**1f**	H	F	74	95:5
7	**1g**	H	OCH_3	72	95:5
8	**1h**	OH	H	77	95:5
9	**1i**	1-Naphthylamine[e]		72	96:4

[a] All reactions were conducted at room temperature in acetonitrile using 10 mol% $BiCl_3$ and completed in 30 min.
[b] The products were characterized by MS, IR, ^1H, ^{13}C NMR and NOESY spectroscopy.
[c] Yield refers to the mixture of diastereomers of products isolated after column chromatography.
[d] Product ratio is based on isolation by column chromatography.
[e] 1-Naphthylamine was used in place of the substituted aniline.

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References

1. Reviews: (a) Boger, D. L.; Weinberg, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: Orlando, 1987; Chapters 2 and 9; (b) Weinberg, S. M. In *Heterodienophile Additions to Dienes*; Trost, B. M.; Fleming, I., Eds.; Comprehensive organic synthesis; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.2, p. 401; (c) Tietze, L. F.; Keltschan, G. *Top. Curr. Chem.* **1997**, *189*, 1; (d) Motorina, I. A.; Grierson, D. S. *Tetrahedron Lett.* **1999**, *40*, 7211; (e) Motorina, I. A.; Grierson, D. S. *Tetrahedron Lett.* **1999**, *40*, 7215.
2. (a) Kiselyov, A. S.; Armstrong, R. W. *Tetrahedron Lett.* **1997**, *38*, 6163; (b) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462; (c) Yadav, J. S.; Reddy, B. V. S.; Madhuri, C.; Sabitha, G. *Synthesis* **2001**, *7*, 1065; (d) Jones, W.; Kiselyov, A. S. *Tetrahedron Lett.* **2000**, *41*, 2309.
3. (a) Kiselyov, A. S.; Smith, L.; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 5089; (b) Kiselyov, A. S.; Smith, L. S.; Virgilio, A.; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 7987; (c) Kiselyov, A. S.; Zhang, D. *Synlett* **2001**, *7*, 1173.
4. (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031 and references cited therein; (b) Johnson, J. V.; Ranckman, S.; Baccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942; (c) Yamada, N.; Kadowaki, S.; Takahashi, K.; Mezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211; (d) Faber, K.; Stueckler, H.; Kappe, T. *Heterocycl. Chem.* **1984**, *21*, 1177.
5. (a) Johnson, J. V.; Raukman, S.; Baccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942; (b) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Baker, R.; Forster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R. *J. Med. Chem.* **1992**, *35*, 1942; (c) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmcol.* **1992**, *44*, 1211; (d) Faber, K.; Stueckler, H.; Kappe, T. *Heterocycl. Chem.* **1984**, *21*, 1177.
6. Faulkner, D. *J. Nat. Prod. Rep.* **1986**, *3*, 1.
7. (a) *Tetrahydrochromano[4,3-b]quinolines*: Sabitha, G.; Venkata Reddy, E.; Yadav, J. S. *Synthesis* **2001**, *10*, 1979; (b) *Hexahydrodibenzo[b,h][1,6]naphthyridines*: Sabitha, G.; Venkata Reddy, E.; Maruthi, Ch.; Yadav, J. S. *Tetrahedron Lett.* **2002**, *43*, 1573; (c) *Octahydroacridines*: Sabitha, G.; Venkata Reddy, E.; Yadav, J. S. *Synthesis* **2002**, in press.
8. Hultin, P. G.; Earle, M. A.; Sudarshan, M. *Tetrahedron* **1997**, *53*, 14823.
9. Review: (a) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249; (b) Vidal, S. Synlett Spotlight 31, *Synlett* **2001**, 1194.
10. Sharma, G. V. M.; Srinivas Reddy, I.; Goverdhan Reddy, V.; Rama Rao, A. V. *Tetrahedron: Asymmetry* **1999**, *10*, 229.
11. **General procedure**: $BiCl_3$ (10 mol%) was added to a mixture of amine **1** (1 mmol) and the *O*-allyl derivative of sugar aldehyde **2** (1.1 mmol) in 5 mL of acetonitrile. The reaction mixture was stirred at room temperature in acetonitrile for 30 min. On completion as indicated by TLC, the reaction mixture was filtered through Celite and the filtrate was taken into ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product was chromatographed on silica gel (EtOAc/hexane, 2:98) to afford **3** and **3′** in 71–81% yield. Selected analytical data for compound **3d** (*trans*): Mp 238–242°C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.09 (s, 3H, Me-D), 1.34 (s, 3H, Me-A), 1.36 (s, 3H, Me-C), 1.56 (s, 3H, Me-B), 2.02 (td, 1H, $J_{11a-5a}=11.3$, $J_{5a-5'\ (pro-R)}=11.3$, $J_{5a-5\ (pro-S)}=3.6$ Hz, H-5a), 2.21 (s, 3H, Ar-CH_3), 3.29 (t, 1H, $J_{5a-5'\ (pro-R)}=11.3$ Hz, $J_{5\ (pro-S)-5'\ (pro-R)}=11.3$ Hz, H-5′), 3.54 (dd, 1H, $J_{11b-11a}=3.5$ Hz, $J_{11a-5a}=11.3$ Hz, H-11a), 4.02 (d, 1H, $J_{3b-11b}=1.7$ Hz, H-3b), 4.05 (dd, 1H, $J_{5a-5\ (pro-S)}=3.6$ Hz, $J_{5\ (pro-S)-5'\ (pro-R)}=11.3$ Hz, H-5), 4.38 (brs, 1H, NH), 4.43 (dd, 1H, $J_{3b-11b}=1.7$ Hz, $J_{11b-11a}=3.5$ Hz, H-11b), 4.50 (d, 1H, $J_{12a-3a}=3.7$ Hz, H-3a), 5.95 (d, 1H, $J_{12a-3a}=3.7$ Hz, H-12a), 6.88 (s, 1H, ArH), 7.06 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 25.9, 26.5, 26.9, 27.0,

33.7, 39.1, 50.0, 66.1, 75.0, 79.6, 83.3, 105.2, 109.6, 111.5, 125.8, 127.2, 130.5, 132.1, 137.2; IR (KBr) 3405, 2950, 1496, 1088 cm^{-1}; MS (*m*/*e*): 425 (M+1).

Selected analytical data for compound **3′d** (*cis*): Mp 208–210°C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (s, 3H, Me-C), 1.33 (s, 3H, Me-D), 1.34 (s, 3H, Me-A), 1.56 (s, 3H, Me-B), 1.99 (dt, 1H, $J_{11a-5a}=4.1$ Hz, $J_{5a-5\ (pro-S)}=4.1$ Hz, $J_{5a-5'\ (pro-R)}=11.6$ Hz, H-5a), 2.20 (s, 3H, Ar-CH_3), 3.18 (t, 1H, $J_{5a-5'\ (pro-R)}=11.6$ Hz, $J_{5\ (pro-S)-5'\ (pro-R)}=11.6$ Hz, H-5′), 3.70 (dd, 1H, $J_{5a-5\ (pro-S)}=4.1$ Hz, $J_{5\ (pro-S)-5'\ (pro-R)}=11.6$ Hz, H-5), 4.05 (dd, 1H, $J_{11a-5a}=4.1$ Hz, $J_{11b-11a}=2.8$ Hz, H-11a), 4.07 (dd, 1H, $J_{11b-11a}=2.8$ Hz, $J_{3b-11b}=2.1$ Hz, H-11b), 4.11 (d, 1H, $J_{3b-11b}=2.1$ Hz, H-3b), 4.20 (brs, 1H, NH), 4.47 (d, 1H, $J_{3a-12a}=3.6$ Hz, H-3a), 5.94 (d, 1H, $J_{12a-3a}=3.6$ Hz, H-12a), 6.80 (s, 1H, ArH), 7.05 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 25.6, 26.1, 26.75, 29.67, 33.5, 33.6, 38.9, 45.5, 62.9, 75.6, 78.2, 83.5, 108.3, 111.7, 125.5, 127.25, 129.7, 130.5, 136.1. IR (KBr) 3417, 2927, 1499, 1089 cm^{-1}; MS (*m*/*e*): 425 (M+1).

12. Minimum energy calculations were carried out on a Silicon graphics O_2 workstation, using SYBYL 6.8. Tripos force field with default parameters used throughout the simulations. The structures were energy minimized using Steepest Descent, followed by Conjugate Gradient methods for a maximum of 1000 iterations or RMS deviation of 0.05 kcal mol^{-1}, whichever was earlier. The derived energy minimized structures were finally normalised geometrically with AM1 algorithm using MOPAC.