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Azabicyclo[3.1.0]hexane-1-ols as frameworks for the asymmetric synthesis of biologically active compounds

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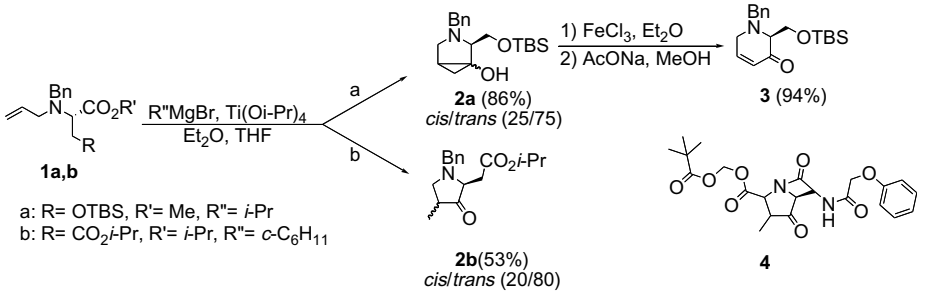
Abstract—Azabicyclo[3.1.0]hexane-1-ols, easily obtained by Ti(IV)-mediated cyclopropanation of amino acid derivatives, constitute versatile, and unprecedented intermediates for the asymmetric synthesis of pharmacologically active products. Indeed, through selective rearrangement, these compounds undergo unusual ring cleavage to lead to pyrrolidinones. Fe(III)-promoted ring opening followed by basic dehydrohalogenation furnishes optically active dihydropyridinones, while Ce(IV)-promoted ring opening provides chiral tricyclopiperidinones via a radical process.

Recently, the titanium(IV)-mediated cyclopropanation of esters by Grignard reagents (Kulinkovich reaction[1]) was extended to the case of ω-allyl esters to provide fused bicyclic cyclopropanols, used in the synthesis of bioactive natural products.[2]

Previously, Sato and co-workers[3] have also successfully applied this method to synthesize the azabicyclo[3.1.0]-hexane-1-ol **2a** from the serine derivative **1a**. A selective ring opening of the cyclopropane moiety carried out on the mixture of **2a** diastereomers furnished 3-piperidinone **3** with 98% ee.

However, we found that a similar experiment carried out on the aspartic acid derivative **1b** directly led to the pyrrolidinone **2b** as an inseparable mixture of diastereomers[4] through an unconventional ring opening of cyclopropanol (Scheme 1). The **2b** skeleton can be considered as a plausible precursor of some active pharmacological products, such as carbapene **4**.[5] Here, to prove that the aspartic acid derivative constitutes an exception in the cyclopropanation reaction, we have prepared esters **5a′**–**e′** from the amino acids alanine **5a** (R = CH_3), valine **5b** (R = $CH(CH_3)_2$), leucine **5c** (R = *i*-Bu), isoleucine **5d** (R = *s*-Bu), and phenylglycine **5e** (R = Ph). The



Scheme 1.

Keywords: Azabicyclo[3.1.0]hexan-1-ol; Pyrrolidinone; Dihydropyridinones; Piperidinones.
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aminoesters **5a′–e′** were N-allylated[6] to give amines **6a–e**, which were then N-benzylated[7] to afford the corresponding ester derivatives **7a–e** (Scheme 2).

All products were then submitted to Ti(IV)-mediated cyclopropanation, which furnished the azabicyclo[3.1.0]-hexane-1-ols **8a–e** as mixtures of cis and trans diastereomers in good yields (Scheme 3).

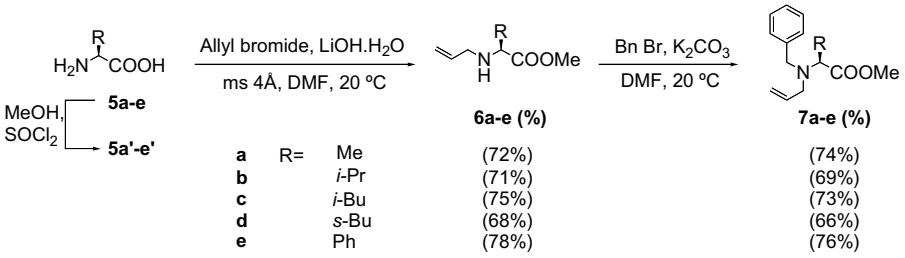
It was noteworthy that, in contrast with the inseparable isomeric mixture prepared by Sato from a serine derivative, azabicyclo[3.1.0]hexane-1-ol stereomers **8a–e** were separated by silica gel chromatography and the relative cis and trans configurations were determined for each by NOESY two-dimensional NMR experiments.

Furthermore, even as a diastereomeric mixture, the azabicyclo[3.1.0]hexane-1-ol **8e** is a precursor for the synthesis of NK1 antagonists.[8] Application of the Saegusa procedure to cyclopropanols **8a–e** yielded dihydropyridinones **9a–e**, compounds which present potential inhibitory activities toward γ-secretase.[9]

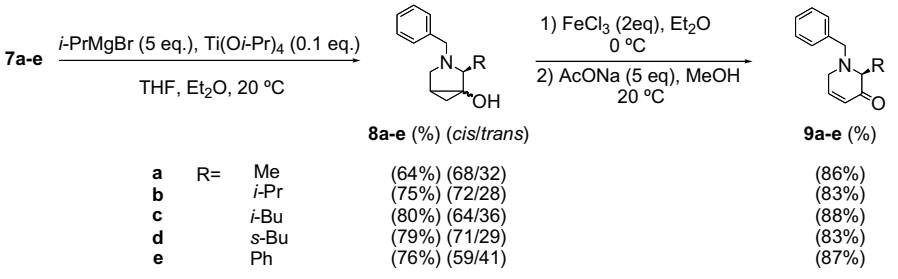
More recently, Flower II and co-workers[10] showed that bicyclo[4.1.0]hexanol furnished β-substituted cycloheptanones via CAN promoted ring opening in the presence of N_3^-, I^-, and Br^-.

Surprisingly, following the same protocol, azabicyclo[3.1.0]hexane-1-ols **8a–e** furnished, respectively, products **10a–e**, whatever the nucleophile used (NaN_3, NaI, and KBr). Moreover, as depicted in Scheme 4, an internal radical process, similar to that reported by Snider,[11] allowed these chiral piperidinones **10a–e** to be synthesized. The structure of the tricyclic piperidinone **10e** was confirmed by X-ray crystal structure analyses. The tricyclic skeleton of compound **10e** is present in inhibitors of biogenic amine transporters.[12]

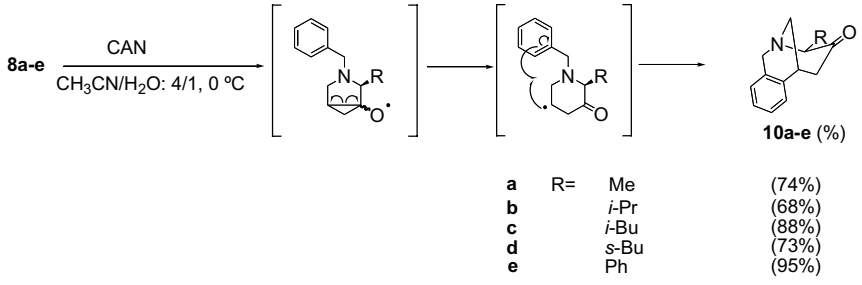
In summary, we have shown the high potential of azabicyclo[3.1.0]hexane-1-ols to provide original chiral products, which can be considered as precursors of bioactive products. Extension of this methodology to other related compounds is under current investigation.



Scheme 2.



Scheme 3.



Scheme 4.

Selected data: Compound **8e**-*cis*: (1*S*,2*S*,5*R*)-3-benzyl-2-phenyl-3-azabicyclo[3.1.0]hexan-1-ol: colorless oil. $[\alpha]_D^{20}$ −9.3 (*c* 0.5, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ 0.93 (t, $J = 4.7$ Hz, 1H), 1.21 (dd, $J = 9.0$, 4.7 Hz, 1H), 1.28 (br s, 1H), 1.71–1.75 (m, 1H), 2.74 (d, $J = 9$ Hz, 1H), 3.15 (dd, $J = 9.0$, 4.0 Hz, 1H), 3.39 (AB system, $\delta_{vAB} = 39.6$ Hz, $J_{AB} = 14.0$ Hz, 2H), 4.20 (s, 1H), 7.15–7.42 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.0, 23.9, 52.9, 54.7, 64.7, 69.2, 126.9, 127.7, 128.2, 128.4, 128.6, 128.7, 138.4, 139.9. FT-IR (NaCl, cm^{-1}) 3377, 3028, 2799, 1602. MS (EI) *m*/*z* (%) 265 (6) [$M^{+\cdot}$], 237 (19), 194 (24), 92 (25), 91 (100), 65 (16). HRMS *m*/*z* calcd for $C_{18}H_{19}NO$: 265.1461. Found: 265.1474.

Compound **8e**-*trans*: (1*R*,2*S*,5*S*)-3-benzyl-2-phenyl-3-azabicyclo[3.1.0]hexan-1-ol: white solid. Mp 110 °C. $[\alpha]_D^{20}$ −50.1 (*c* 0.5, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ 0.69 (dd, $J = 9.0$, 4.7 Hz, 1H), 1.28 (br s, 1H), 1.29 (t, $J = 4.7$ Hz, 1H), 1.58–1.63 (m, 1H), 2.61 (dd, $J = 9.0$, 4.0 Hz, 1H), 2.90 (d $J = 9.0$ Hz, 1H), 3.52 (AB system, $\delta_{vAB} = 219.6$ Hz, $J_{AB} = 13.3$ Hz, 2H), (d, $J = 13.3$ Hz, 1H), 3.83 (d, $J = 13.3$ Hz, 1H), 3.86 (s, 1H), 7.15–7.42 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.0, 23.9, 52.9, 54.7, 64.7, 69.2, 126.9, 127.7, 128.2, 128.4, 128.6, 128.7, 138.4, 139.9. FT-IR (NaCl, cm^{-1}) 3377, 3028, 2799, 1609. MS (EI) *m*/*z* (%) 265 (9) [$M^{+\cdot}$], 237 (22), 194 (13), 118 (35), 116 (37), 91 (100), 64 (15), 41 (53). HRMS *m*/*z* calcd for $C_{18}H_{19}NO$: 265.1461. Found: 265.1451.

Compound **9e**: (2*S*)-1-benzyl-2-phenyl-1,6-dihydropyridin-3(2*H*)-one. Colorless oil. $[\alpha]_D^{20}$ −74.2 (*c* 0.8, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 3.27 (ddd, $J = 19.5$, 3.6, 2.1 Hz, 1H), 3.52 (ddd, $J = 19.5$, 3.6, 2.1 Hz, 1H), 3.55 (d, $J = 13.5$ Hz, 1H), 3.74 (d, $J = 13.5$ Hz, 1H), 4.30 (s, 1H), 6.30 (dt, $J = 10.2$, 2.0 Hz, 1H), 7.04 (dt, $J = 10.2$, 3.6 Hz, 1H), 7.27–7.43 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 48.6, 58.5, 72.6, 127.4, 128.1, 128.2, 128.5, 128.6, 128.7, 128.9, 136.4, 137.8, 147.8, 196.4. FT-IR (NaCl, cm^{-1}) 3030, 2765, 1682, 1628, 1602. MS (EI) *m*/*z* (%) 263 (4) [$M^{+\cdot}$], 196 (75), 194 (36), 172 (100), 92 (15). HRMS *m*/*z* calcd for $C_{18}H_{17}NO$: 263.1305. Found: 263.1299.

Compound **10e**: (1*R*,10*S*)-10-phenyl-9-azatricyclo-[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-11-one: white solid. Mp 80 °C. $[\alpha]_D^{20}$ +272 (*c* 0.5, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ 2.49 (dd, $J = 14.1$, 1.8 Hz, 1H), 2.85 (dd, $J = 14.1$, 4.2 Hz, 1H), 3.25 (d, $J = 13.5$ Hz, 1H), 3.27 (m, 1H), 3.60 (d, $J = 13.5$ Hz, 1H), 4.05 (d, $J = 17.7$ Hz, 1H), 4.39 (s, 1H), 4.72 (d, $J = 17.7$ Hz, 1H), 7.06–7.51 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 37.6, 46.1, 47.3, 57.5, 76.2, 126.3, 127.1, 127.3, 127.6, 128.5, 128.8, 133.4, 136.0, 138.1, 211.7. FT-IR (NaCl, cm^{-1}) 3025, 2933, 2253, 1710. MS (EI) *m*/*z* (%) 263 (5) [$M^{+\cdot}$], 235 (100), 234 (49), 131 (30), 118 (33), 115 (30), 91 (95), 88 (90). HRMS (ES) *m*/*z* calcd for $[C_{18}H_{17}NO+H]^+$: 264.1383. Found: 264.1390.

CCDC 653757 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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