An Enantioselective Synthetic Route to cis-2,4-Disubstituted and 2,4-Bridged Piperidines

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A synthetic route to enantiopure cis-2,4-disubstituted and 2,4-bridged piperidines is reported, the key step being a stereoselective conjugate addition of an organocuprate to a phenylglycinol-derived unsaturated lactam bearing a substituent at the 8a-position.

Aminoalcohol-derived oxazolopiperidone lactams are exceptionally versatile building blocks for the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds.1 These lactams allow the substituents to be introduced at the different ring positions in a regio- and stereocontrolled manner, providing easy access to enantiopure polysubstituted piperidines bearing virtually any type of substitution pattern.2 In particular, the conjugate addition to α,β-unsaturated oxazolopiperidone lactams allows the stereocontrolled formation of a C–C bond at the piperidine 4-position, and has successfully been used to generate either cis or trans 3,4-disubstituted enantiopure piperidine-containing derivatives, including the antidepressant drug (+)-paroxetine,3 cis-fused perhydrocycloalka[c]pyridines,4 and the indole alkaloid (+)-uleine.5

To further expand the potential of these lactams we decided to explore a synthetic route to enantiopure 2,4-bridged piperidine derivatives, as outlined in Scheme 1. The key step would be the stereocontrolled introduction of an appropriate unsaturated chain at the 4-position of the piperidine ring by conjugated addition of an organocuprate to an unsaturated lactam A bearing an unsaturated substituent at the 2-position. A subsequent ring-closing metathesis from the resulting cis-2,4-disubstituted piperidine derivative would lead to the target bridged azabicyclo.

SCHEME 1. Synthetic Strategy

It has previously been established6 that the conjugate addition of organocuprates to unsaturated oxazolopiperidone lactams B (when R = H) is highly stereoselective as a consequence of the conformational rigidity of the bicyclic system. The nucleophilic attack occurs under stereoelectronic control7 on the exo face, axial to the electrophilic carbon of the conjugate double bond (Figure 1).8 However, it could be expected a priori that the presence of a substituent at the angular position (R ≠ H) could alter the stereochemical outcome of the conjugate addition as a consequence of the 1,3-syn diaxial interactions between this substituent and the incoming nucleophile. For this reason, to evaluate the viability of our synthetic plan we decided to carry out a preliminary study on the stereoselectivity of similar conjugate addition reactions from the model, more easily accessible, unsaturated lactams 3a and 3b. These lactams were prepared,9 via the corresponding selenides 2 (diastereomeric mixtures), from the known lactams 1a and 1b10 (Scheme 2). The easily removable benzylxy-carbonyl electron-withdrawing group was used to enhance the reactivity of the conjugated system.12

FIGURE 1. Stereoelectronic control in the conjugate addition.

The conjugate addition of a vinyl group to lactam 3a was satisfactorily accomplished (62% overall yield from 2a) with vinylmagnesium bromide in the presence of LiCl, Cul, and trimethylsilyl chloride13 in THF. The high exo facial stereoselectivity of the conjugate addition was confirmed after removal of the benzylxy-carbonyl substituent present in 4a by hydrogenolysis, which took place with simultaneous hydrogenation of the vinyl group, followed by thermal decarboxylation. Under these conditions a 93:7 mixture
(calculated by NMR) of lactam 7a and its C-7 epimer was obtained (see Table 1).

SCHEME 2. Conjugate Addition to 8a-Substituted Unsaturated Oxazolopiperidone Lactams

Under the same conditions the sterically more demanding 8a-phenyl substituted lactam 3b gave a similar result: the conjugate addition of a vinyl residue took place in 61% yield (from 2b) and the subsequent debenzyloxy carbonylation afforded (73%) a 94:6 diastereomeric mixture of 7b and its C-7 epimer.

Similar conjugate additions of allylmagnesium chloride to unsaturated lactams 3a and 3b took place with lower stereoselectivity and, after removal of the benzoxycarbonyl group as in the above series, lactams 8a and 8b were obtained along with the corresponding C-7 epimers (78:22 and 85:15 ratio, respectively) in acceptable overall yield (50% from 2a; 65% from 2b).

A moderate stereoselectivity was also observed in the conjugate addition of the organocinate derived from phenylmagnesium chloride to 3a: a 84:16 mixture of lactam 9a and its C-7 epimer was isolated in 51% overall yield from 2a.

In contrast, somewhat surprisingly, the conjugate addition of this organocinate to the 8a-phenyl substituted lactam 3b took place in excellent yield and very high exo stereoselectivity (Table 1), ultimately leading to lactam 9b in 60% overall yield (from 2b). A π-stacking interaction between the incoming- and 8a-phenyl groups could account for the high stereoselectivity.

<table>
<thead>
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<th>TABLE 1. Conjugate Addition Reactions from Unsaturated Lactams 3</th>
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<sup>a</sup> Overall yield from selenides 2. * Calculated by NMR after debenzyloxy carbonylation.

To illustrate the synthetic usefulness of the above methodology, the phenyl-substituted lactams 9a and 9b were converted to enantiopure cis-2,4-disubstituted piperidines as shown in Scheme 3. Thus, treatment of lactams 9 with LiAlH<sub>4</sub> brought about both the reduction of the amide carbonyl group and the reductive opening of the oxazolidine ring, which took place with complete retention of configuration,<sup>4</sup> to give piperidines 10a and 10b. The cis-relationship of the piperidine substituents at C-2 and C-4 in 10 was evident from the multiplicity of the axial 2 and 4 protons in the NMR spectra (see Supporting Information), thus confirming the stereochemical outcome of the above conjugate additions. A subsequent debenzylisation in the presence of (Boc)O gave enantiopure piperidines 11a and 11b.

SCHEME 3. Synthesis of Enantiopure cis-2,4-Disubstituted Piperidines

The above results made evident that the presence of a substituent at the angular 8a-position has little effect on the stereoselectivity of the conjugate addition. However, to access bridged piperidine derivatives following the strategy outlined in Scheme 1, we decided to take advantage of the higher stereoselectivity of the vinyl conjugate additions and chose starting lactams A bearing an allyl or 3-butyl substituent at the 8a-position, which should ultimately lead to 6,6 and 6,7 bridged azacyclic systems, respectively.

The synthetic sequence is outlined in Scheme 4. The required unsaturated lactams 14<sup>10</sup> were prepared from lactams 12a<sup>11</sup> and 12b<sup>12</sup> via the corresponding selenides 13. As could be expected from the above model experiments, the conjugate addition of the organocinate derived from vinylmagnesium bromide to crude lactams 14 took place in good yield (~60% from 13) and excellent facial diastereoselectivity to give the exo compounds 15 as C-6 epimeric mixtures (only trace amounts of C-7 endo epimers were detected by NMR), which were directly cyclized (~80% yield) in the presence of the second generation Grubs catalyst.<sup>13</sup> A subsequent catalytic hydrogenation of the resulting bridged derivatives 16 brought about both the reduction of the C–C double bond and debenzylisation to lead, after thermal decarboxylation, to...
tricyclic lactams 17a (78%) and 17b (83%). In the 6,7 bridged series, lactam 17b was converted to the enantiopure 7-
azaazabicyclo[4.3.1]decanec (B-homomorphan) 19b (58% overall yield) by alane reduction followed by hydrogenolysis in
presence of (Boc)2O. However, in 17a the reductive cleavage of the C-O bond of the oxazolidine ring was more difficult, probably because the process involves the bridgehead carbon of a 6,6 bridged system. In this series, alane reduction of 17a caused only the reduction of the lactam carbonyl. A subsequent prolonged (48 h) treatment of the resulting tricyclic amine with Et3SiH-TiCl3 led to bicyclic amine 18a (48% overall yield from 17a), which was then converted to the enantiopure 2-azaazabicyclo[3.3.1]nonane (morphan) 19a as in the above 6,7 bridged series. Alternatively, in the B-

homomorphan series, tricyclic lactam 17b was converted to lactam 21 in two steps (65% overall yield) as depicted in

Scheme 4.

**SCHEME 4. Synthesis of Enantiopure 2-
Azaazabicyclo[3.3.1]nonanes and 7-Azaazabicyclo[4.3.1]decanes**

In summary, the exo facial stereoselectivity observed in the conjugate addition of organocuprates to 8a-unsaturated unsaturated oxazolopiperidone lactams B (R = H) is maintained in the 8a-substituted derivatives, in particular when the incoming group is vinyl. By choosing the appropriate substituent at the 8a position in the starting oxazolopiperidone and the appropriate organocuprate in the conjugate addition step, the reported methodology provides a versatile route to enantiopure cis-2,4-disubstituted and 2,4-
bridged piperidines.20

**Experimental Section**

**General Procedure for the Conjugate Addition to Unsaturated Lactams (with 4a as an example).** LiCl (189 mg, 4.5 mmol) was heated at 80 °C for 1 h under vacuum (10-15 mm Hg) in a three-necked, 500 mL round-bottomed flask. Then, Cul (357 mg, 4.5 mmol) and THF (5 mL) were added at rt, and the mixture was stirred at rt for 5 min. The suspension was cooled at ~78 °C, and vinylmagnesium bromide (1 M in THF, 4.5 mL). TMSCl (0.57 mL, 4.5 mmol), and the crude of unsaturated lactam 3a (1.8 mmol) in THF (8 mL) were successively added. The resulting mixture was stirred at ~78 °C for 20 h. The reaction was quenched with saturated aqueous NH4Cl, and the organic layer was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (1:4 EtOAc-hexane) gave lactams 4a (major) and 7-epi-4a as mixtures of C-6 epimers (508 mg, 62% overall yield from 2a). 4a (major C-6 epimer): IR (NaCl) 1665, 1744 cm⁻¹; ¹H NMR (400 MHz, CDCl3, COSY, HETCOR) δ 1.54 (s, 3H, CH3), 1.94 (dd, J = 14.4, 8.4 Hz, 1H, H-8), 2.38 (dd, J = 14.4, 7.2 Hz, 1H, H-8), 3.15 (m, 1H, H-7), 3.40 (d, J = 10.8 Hz, 1H, H-6), 4.03 (dd, J = 9.2, 6.8 Hz, 1H, H-2), 4.41 (t, J = 8.4 Hz, 1H, H-2), 5.09 (m, 2H, CH2=C), 5.17 (d, J = 12.4 Hz, 1H, CH, benzyl), 5.24 (d, J = 12.4 Hz, 1H, CH, benzyl), 5.42 (t, J = 7.2 Hz, 1H, H-3), 5.74 (ddd, J = 17.2, 10.4, 7.2 Hz, 1H, CH=C), 7.25-7.36 (m, 10H ArH); ¹³C NMR (100 MHz, CDCl3) δ 26.7 (CH3), 36.0 (C-7), 39.5 (C-8), 53.7 (C-6), 59.1 (C-3), 67.0 (CH2, benzyl), 69.2 (C-2), 93.2 (C-8a), 116.5 (CH=C=), 124.5-128.5 (C-o, m, p), 135.6, 139.7 (C-i), 138.1 (CH=C=), 166.7 (NCO), 168.7 (COO). Anal. Caled for C18H23NO2: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.30; H, 6.58; N, 3.51.

**General Procedure for the Ring-closing Metathesis Reaction (with 16a as an example).** Second-generation Grubbs catalyst (3 mg) was added to a solution of lactams 15a (20 mg, 0.05 mmol) in CH2Cl2 (7 mL). The mixture was stirred at rt for 2 h, concentrated, and purified by flash column chromatography (1:9 to 1:4 EtOAc-hexane) to yield tricyclic lactam 16a as a mixture of C-6 epimers (ratio 2:1, 16 mg, 80% yield). 16a (major): IR (NaCl) 1659, 1734 cm⁻¹; ¹H NMR (400 MHz, CDCl3, HETCOR) δ 2.30-2.45 (m, 3H, 2H-10, CH3), 2.35 (dd, J = 12.0, 4.0 Hz, 1H, CH3), 3.24 (d, J = 4.0 Hz, 1H, H-7), 3.67 (d, J = 6.4 Hz, 1H, H-6), 4.00 (t, J = 8.8 Hz, 1H, H-2), 4.61 (t, J = 8.4 Hz, 1H, H-2), 5.18 (d, J = 12.4 Hz, 1H, CH, benzyl), 5.22 (d, J = 12.4 Hz, 1H, CH, benzyl), 5.48 (t, J = 8.0 Hz, 1H, H-3), 5.64 (m, 1H, CH=C=), 5.76 (m, 1H, CH=), 7.05-7.20 (m, 10H, ArH); ¹³C NMR (100 MHz, CDCl3) δ 31.8 (C-10), 34.4 (C-7), 36.1 (CH3), 52.0 (C-6), 58.7 (C-3), 67.2 (CH2, benzyl), 70.1 (C-2), 92.3 (C-11), 125.0-129.9 (C-o, m, p, CH=C=), 135.4, 139.2 (C-i), 164.2 (NCO), 169.7 (COO). 16a (minor): ¹H NMR (400 MHz, CDCl3, selected resonances) δ 2.19 (ddd, J = 12.4, 4.4, 1.6 Hz, 1H, H-10), 3.05 (br, 1H, H-7), 3.53 (s, 1H, H-6), 4.02 (dd, J = 9.2, 7.6 Hz, 1H, H-2), 4.57 (t, J = 8.8 Hz, 1H, H-2), 5.45 (t, J = 7.6 Hz, 1H, H-3), 5.76.
(m, 1H, CH=), 5.90 (m, 1H, CH=); $^{13}$C NMR (100.6 MHz, CDCl$_3$, selected resonances) δ 30.9 (C-10), 33.3 (C-7), 36.2 (CH$_3$), 53.5 (C-6), 57.9 (C-5), 67.0 (CH$_2$ benzyli), 70.1 (C-2), 92.4 (C-11), 164.5 (NCO), 168.9 (COO); HRMS calcd for [C$_2$H$_3$NO$_2$ + H]$^+$: 390.1699, found: 390.1704.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all compounds, and copies of $^{1}$H and $^{13}$C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References


10. Unsaturated lactams 3 and 14 are acid and base sensitive and must be prepared immediately before the next reaction and used without further purification.


14. For a discussion on the stereochemical outcome in the reduction of 8a-substituted ozaoxolopiperidone lactams, see reference 11b and references cited therein.

15. Lactam 12a was prepared in three steps (1. H$_2$, Pd/C; 2. n-Bu$_2$P, o-NO$_2$(C$_6$H$_4$)SeCN; 3. H$_2$O$_2$, Pyr.; 40% overall yield) from the known$^{16}$ 8a-benzoxoypropyl substituted lactam.

16. (a) Lactam 12b was prepared in 57% yield by cyclocondensation of (R)-phenylglycinol with the known$^{16}$ 5-oxo-8-nonenenoic acid. (b) Mazur, P.; Nakanishi, K. J. Org. Chem. 1992, 57, 1047–1051.

