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Asymmetric synthesis of quaternary tetrahydroisoquinoline-3-carboxylic acid derivatives

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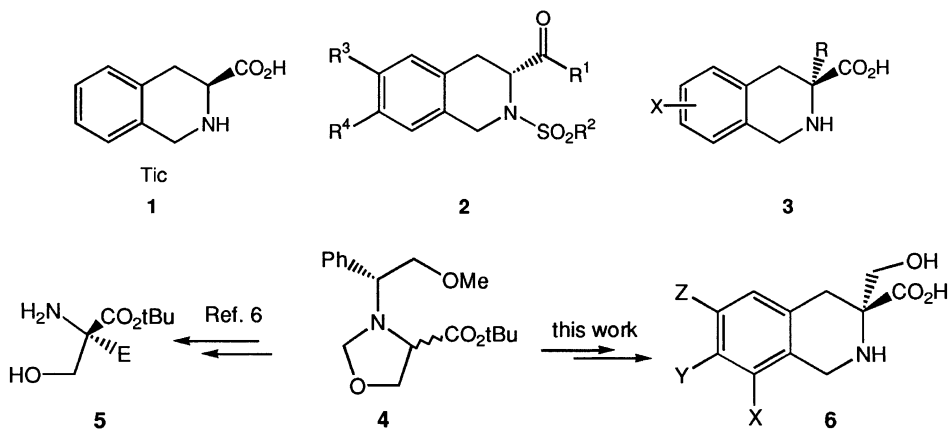
Abstract—A new route towards the asymmetric preparation of quaternary 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives has been developed. The key step involves an intramolecular Pictet–Spengler reaction of an oxazolidino ester.

The design of new unnatural conformationally restricted α-amino acids has been a popular area of endeavor in recent years.[1] Incorporation of such derivatives into peptidic or non-peptidic structures can usually bring new insights into SAR analysis, and lead to the development of compounds with improved pharmacological profiles. Among the numerous constrained analogs reported in the literature, tetrahydroisoquinoline carboxylic acid (Tic) derivatives are of particular interest, since they are able to restrain conformational freedom around χ torsion angles.[2] For instance, incorporation of Tic **1** into peptides led to δ opioid receptor antagonists,[3] and compound **2** was used as a molecular scaffold for the design of matrix metalloproteinases.[4] Although α substitution of Tic is believed to produce molecules with even more constrained conformations, examples of asymmetric preparation of derivatives **3** are still scarce.[5]

We recently reported a new method for the asymmetric synthesis of α substituted quaternary serines based on the diastereoselective functionalization of oxazolidine **4** (Scheme 1).[6]

During our studies, we noted that the acidic hydrolysis of such oxazolidines proved to be troublesome, because of the good stability of the transient iminium species. We report in this paper the use of this iminium reactivity for the preparation of tetrahydroisoquinolines **6** via intramolecular Pictet–Spengler reactions.[7]



Scheme 1.

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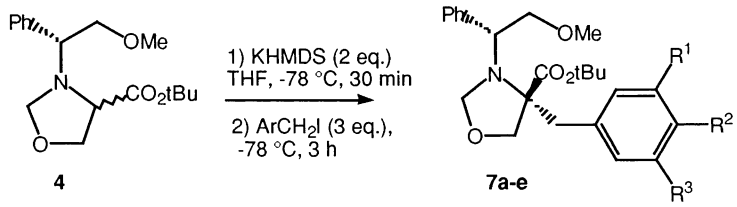
Table 1.



Compound	R^1	R^2	R^3	d.e. (%)[a,b]	Yield (%)[a]
7a	OMe	H	H	94	64
7b	OMe	OMe	H	96	74
7c	OMe	OMe	OMe	95	50
7d	O-CH_2-O		H	94	65
7e	Cl	H	H	86	70

[a] Yield of diastereomer mixture.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Quaternary oxazolidines **7a–e** were prepared from oxazolidine **4** according to our reported procedure (Table 1).[6] They were obtained with good diastereomeric purity, except for compound **7e**. In this case, diastereomerically pure material could be obtained, albeit in a moderate yield (47%) after chromatographic separation. The absolute configuration of the newly created asymmetric center was established according to our previous results with standard electrophiles.[6]

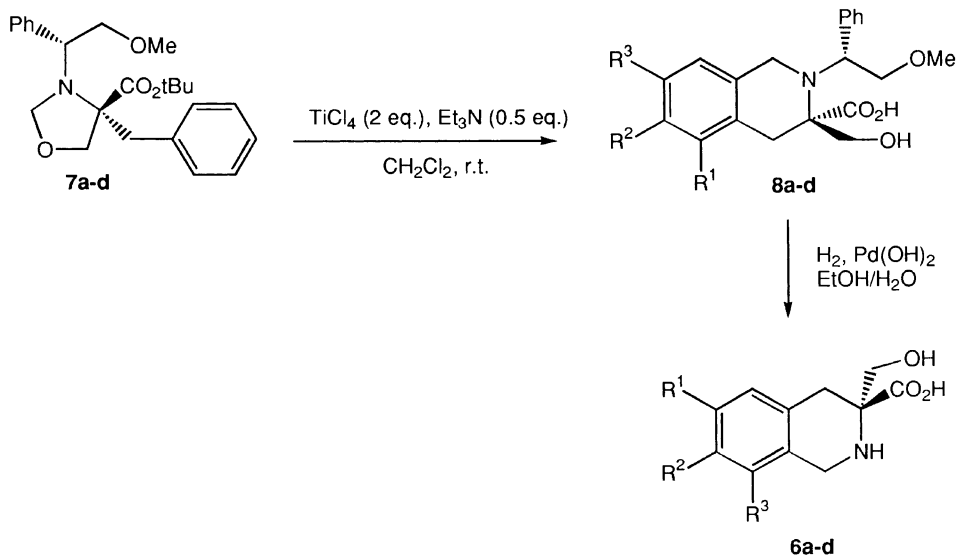
As already noticed, the best yields were obtained with benzylic electrophiles bearing iodine as a leaving group. They were prepared by halogen exchange or from the corresponding alcohol starting with commercially available benzyl derivatives.

Compounds **7a–d** smoothly rearranged into the corresponding tetrahydroisoquinolines **8a–d** in the presence of $TiCl_4$. Hydrolysis of *tert*-butyl ester occurred during the aqueous work-up. The chloro derivative **7e** was unreactive under such experimental conditions (Scheme 2 and Table 2).

Cyclization yields proved to be irreproducible unless a small amount of Et_3N was added to the reaction mixture. We found that protonation of the starting oxazolidine nitrogen completely inhibits the Pictet–Spengler cyclization. Addition of Et_3N neutralizes uncontrolled acidic traces in the reaction mixture, leading to reproducible results.[8]

Compounds **8a–d** proved to be quite unstable, and were directly submitted to hydrogenolysis, leading to quaternary amino acids **6a–d**.[9]

The rearrangement of oxazolidine **8a** was not fully regioselective, and an 80:20 mixture of *para*- and *ortho*-substituted compounds was obtained. This mixture was hydrogenolyzed and the expected amino acid **6a** was obtained as a single regioisomer after recrystallization.



Scheme 2.

Table 2.

Compound	R^1	R^2	R^3	Yield (%)[a]
6a	OMe	H	H	30
6b	OMe	OMe	H	70
6c	OMe	OMe	OMe	96
6d	$O\text{-}CH_2\text{-}O$		H	78

[a] Overall isolated yield from **7**.

In the case of compounds **8b–d**, only one regioisomer was obtained in good overall yield.

In conclusion, oxazolidine **4** proved to be a suitable tool for the asymmetric elaboration of various quaternary tetrahydroisoquinoline carboxylic acids. The key step involved an intramolecular Pictet–Spengler reaction, which proceeded efficiently with activated phenyl rings. Compounds **6a–d** can be used as new scaffolds for incorporation into peptides, and the alcohol function can be exploited for further functionalizations.

Acknowledgements

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7. For a similar strategy, see: Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905–4908.
8. The commercial solution of $TiCl_4$ (1 M in CH_2Cl_2) used for the rearrangement may contain some acidic traces.
9. Typical procedure: Oxazolidine **8d** (68 mg, 0.15 mmol) was dissolved in anhydrous dichloromethane (5 mL) with triethylamine (11 μL, 0.07 mmol) under argon. A solution of $TiCl_4$ (1 M in CH_2Cl_2, 308 μL, 0.31 mmol) was added dropwise and the reaction mixture was stirred for 3 h. Water (5 mL) was then added, the organic layer was extracted and the aqueous layer was washed twice with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The crude reaction mixture (66 mg) was dissolved in a 1:1 water/ethanol mixture (8 mL), $Pd(OH)_2$ (20%, 35 mg) was added and the suspension was stirred under a hydrogen atmosphere for 2.5 h. After filtration and solvent evaporation, the crude reaction mixture was purified (Dowex 50X8, 80–100 mesh, 10 g) to give 30 mg of amino acid **6d** (78%). Compound **6d** (white solid): $[\alpha]_D = -25$ ($c = 1.4$, MeOH). **^{1}H NMR** (CD_3OD, 300 MHz) δ ppm: 6.76 (s, 2H) 6.00 (br. s., 2H), 4.42 (d, $J = 15.4$ Hz, 1H), 4.18 (d, $J = 15.4$ Hz, 1H), 4.04 (d, $J = 11.5$ Hz, 1H), 3.77 (d, $J = 11.5$ Hz, 1H), 3.22 (d, $J = 16.6$ Hz, 1H), 3.02 (d, $J = 16.6$ Hz, 1H). **^{13}C NMR** (CD_3OD, 75.5 MHz) δ ppm: 174.9, 148.9, 148.2, 126.7, 123.2, 109.7, 107.2, 102.5, 66.6, 64.9, 43.9, 32.4. MS (NH_3): 252 (MH^+).