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Synthetic studies towards the octahydro-1*H*-benzo[*f*]pyrrolo[3,2,1-*ij*]quinolines: enantioselective synthesis of (2*R*,3*S*)-2-[(1*S*)-3-(benzyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)propyl]-3-phenylhexahydropyridine

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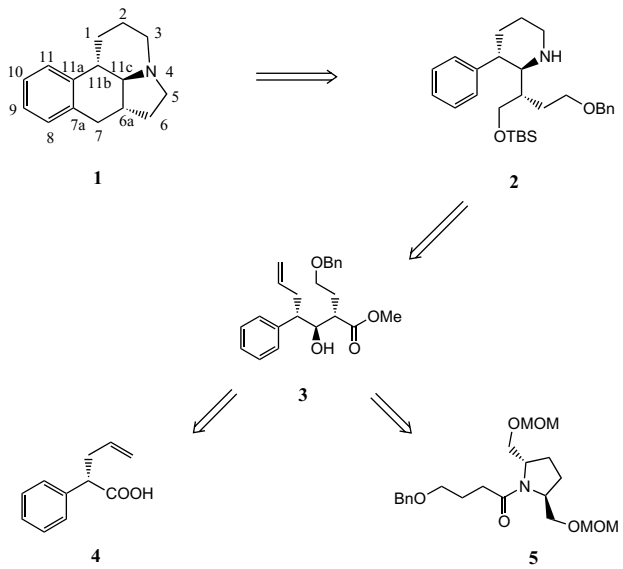
Abstract—(2*R*,3*S*)-2-[(1*S*)-3-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)propyl]-3-phenylhexahydropyridine—a key synthetic intermediate for the preparation of (6a*S*,11b*S*,11c*S*)-1*H*-benzo[*f*]pyrrolo[3,2,1-*ij*]quinoline—was synthesized in nine steps. The synthetic approach uses both enantiomers of the chiral auxiliary *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine, employed in different stages of the synthesis for the construction of two out of the three stereogenic centers in the above mentioned intermediate.

1. Introduction

As part of an ongoing project for the preparation of dopaminergic compounds,[1–3] a number of compounds were designed, based on the structure of 1*H*-benzo[*f*]pyrrolo[3,2,1-*ij*]quinoline (**1**), which incorporates the phenethylamine moiety in its rigid framework. Initial attempts focused on the synthesis of the (6a*S*,11b*S*,11c*S*) enantiomer, which maintains a *trans*/*trans* fusion of the three rings, keeping the phenethylamine moiety in an antiperiplanar conformation, a requirement for dopaminergic activity.[1]

Retrosynthetic ring opening in **1** (Scheme 1) leads to (2*R*,3*S*)-2-[(1*S*)-3-(benzyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)propyl]-3-phenylhexahydropyridine (**2**) which, upon disconnection of a carbon–nitrogen bond leads to methyl (2*S*,3*S*,4*S*)-2-(2-benzyloxyethyl)-3-hydroxy-4-phenyl-6-heptenoate (**3**), which in turn can be further disconnected to (*S*)-2-phenyl-4-pentenoic acid (**4**) and (2*S*,5*S*)-*N*-(4-benzyloxybutyryl)-2,5-bis-(methoxymethoxymethyl)pyrrolidine (**5**).

The synthesis of (*S*)-2-phenyl-4-pentenoic acid (**4**) is depicted in Scheme 2. Reaction of (2*R*,5*R*)-bis-(methoxymethoxymethyl)pyrrolidine[4] with a twofold excess of phenylacetyl chloride and triethylamine (CH_2Cl_2, 0°C) gave amide **6** in 75% yield. The reaction of **6** with 1 equiv. LDA (THF, −78°C) led to an enolate, which according to the literature[5–7] should be



Scheme 1. Retrosynthetic approach to (6a*S*,11b*S*,11c*S*)-1*H*-benzo[*f*]pyrrolo[3,2,1-*ij*]quinoline (**1**).

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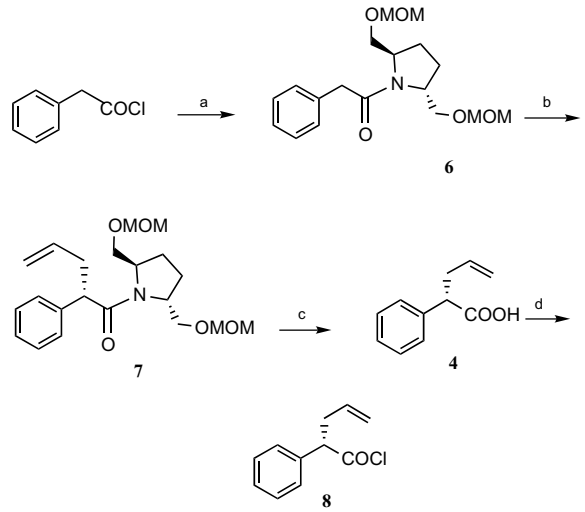


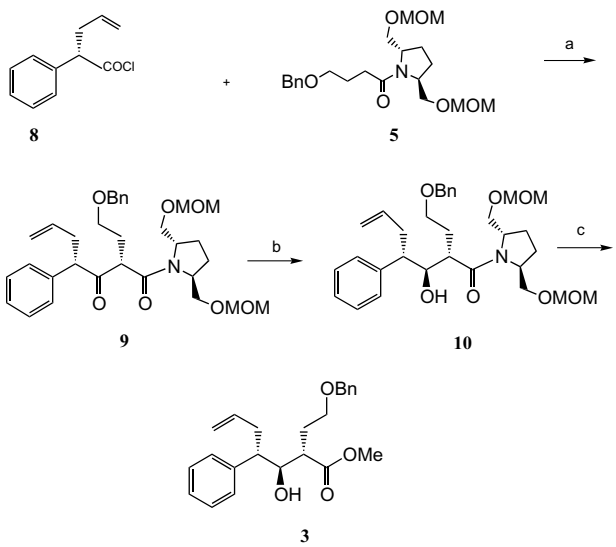
Scheme 2. *Reagents and conditions*: (a) TEA, rt, 12 h, CH_2Cl_2, 78%; (b) allyl bromide, LDA, −78°C, rt, 3 h, 76%; (c) HCl 3N, 3 h, reflux, 72%, 99% ee; (d) $SOCl_2$, rt, 3 h, 100%.

of *Z*-stereochemistry. Addition of allyl bromide and subsequent hydrolysis (3N HCl, reflux, 3 h) of the resulting amide **7** gave (*S*)-2-phenyl-4-pentenoic acid (**4**) in 55% yield from **6** and 99% ee as deduced from an NMR study of the diastereomeric salts of **4** with (*S*)-α-phenethylamine. The proposed (*S*) stereochemistry in **4**, induced by the presence of the (2*S*,5*S*)-auxiliary reagent is in agreement with earlier studies using this chiral reagent for the preparation of similarly α-substituted carboxylic acids.[5] Given the low chemical yield of **4** by this procedure and the need of larger amounts of the reagent, a more efficient alternative synthesis was also used. Alkylation of phenylacetonitrile with allyl bromide[8] (NaOH 12.5N, $BnNEt_3Cl$, 50°C, 3 h) and subsequent hydrolysis (NaOH 12.5N, MeOH, reflux, 8 h) of the nitrile moiety gave racemic **4** in 60% overall yield. Optical resolution of the racemic mixture using (*S*)-α-phenethylamine gave (*S*)-**4** whose optical activity was identical to that of a purified sample from the first preparation, as well as to that reported in the literature ($[\alpha]_D = +102.5$ ($c = 1$, acetone)).[9,10] The corresponding acid chloride **8** was prepared quantitatively upon treatment with thionyl chloride (rt, 3 h).

Reaction of 4-benzyloxybutyric acid with (2*S*,5*S*)-bis-(methoxymethoxymethyl)pyrrolidine[4] (DCC, CH_2Cl_2, 0°C, 12 h), gave amide **5** in 81% yield. The DCC-induced acid-auxiliary amine coupling was used as a more efficient alternative to a direct reaction of the corresponding acid chloride with the amine, since 4-benzyloxybutyryl chloride spontaneously cyclized to butyrolactone.

Coupling of (*S*)-**8** with (2*S*,5*S*)-*N*-(4-benzyloxybutyryl)-2,5-bis(methoxymethoxymethyl)pyrrolidine (**5**) (LDA THF, −78°C, 1 min) in basic media presented a challenge in this synthesis. According to literature data on related asymmetric acylations, affordable yields were obtained only upon addition of an enolate to the acylating agent.[11] This procedure appeared to be problematic in our case given the length of the preparation process of (*S*)-**8** and the practical difficulties in the addition of the lithium enolate of **5** to the reaction mixture. The problem was overcome by addition of 1.1 equiv. of (*S*)-**8** in one portion to the lithium enolate of **5** (THF, −78°C), brief stirring (1 min) of the mixture and quenching by addition of water (Scheme 3). The desired diastereomer **9** was isolated in 84% yield (83% conversion). The diastereoselectivity of the reaction was ca. 97%; a second minor (2%) diastereomer was isolated via column chromatography. The proposed (*S*)-stereochemistry at the acylated carbon is based on the notion that the acylation occurs in the same sense as the alkylation. Although one would expect that the new stereogenic center in β-dicarbonyl compound **9** would easily racemize via enolization, the compound showed a striking stability in weakly acidic and basic solutions. Previous studies on pyrrolidine and oxazolidone β-keto amides report a similar stability of their respective stereogenic centers.[7] This observation could be explained by the fact that the methine hydrogen of the new stereogenic center in **9** lies nearly orthogonal to the π-system of the adjacent imide carbonyl function, due to the minimization of the nonbonding interactions between the chiral auxiliary, and the other two substituents of the stereogenic center.[7]

The next crucial step of the synthesis is the diastereoselective reduction of the keto group to the *anti* hydroxy amide **10**. The use of reagents that may form complexes with the carbonyl moieties would involve a six-membered transition state leading to the undesired *syn* product.[12] Indeed, the use of reagents such as $Zn(BH_4)_2$[13] led to a single diastereomer with a *syn* arrangement of the three groups as indicated by its NMR spectrum. Alternative use of non-complexing, bulky reagents such as KEt_3BH[14] furnished the desired

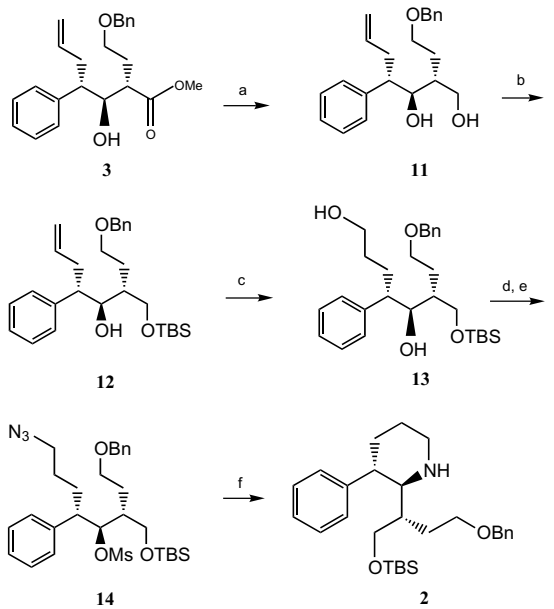


Scheme 3. *Reagents and conditions*: (a) LDA, −78°C, 5 min, 70% >97% ee; (b) $K(Et)_3BH$, 1 h, ether, 0°C, 78%; (c) conc. HCl, MeOH, then NaOH 3N, 60°C, 4 h then TMSCl, MeOH, rt, 15 h, 73%.

anti alcohol in 78% yield. The pyrrolidine auxiliary was then removed in two steps by (a) acidic (MeOH, trace of conc. HCl) cleavage of the MOM protective groups and (b) subsequent basic hydrolysis (3N NaOH, 80°C, 4 h) of the 2,5-bis(hydroxymethyl)pyrrolidine. The resulting acid was esterified (TMSCl, MeOH) without further purification. The white crystalline product **3** was isolated from its diastereomeric byproducts, by flash chromatography, in 73% yield from **10** indicating that in this acid/base removal of the chiral auxiliary, the presence of base did not induce extensive racemization in **10**.[15]

Reduction of the ester group in **3** with $LiAlH_4$ (THF, rt, 3 h) gave diol **11** in 98% yield (Scheme 4). The primary alcohol group was selectively protected as the TBDMS ether (TBDMSCl, imidazole, CH_2Cl_2, 3 h 93%) and the double bond in **12** was then hydroborated (BMS, then 3N NaOH, H_2O_2, 2 h, 70%) to give diol **13**. Mesylation of this material (MsCl, py, CH_2Cl_2, 12 h, 77%) yielded the bis methanosulfonate ester, which was transformed to the azide **14** (LiN_3, DMSO, rt, 6 h) in 60% yield by selective displacement of the primary mesylate by the azide anion.

Reduction of the azide was achieved by hydrogenation over 10% platinum on carbon, to avoid hydrogenolysis of the benzyl ether. Under the reaction conditions (H_2, 10% Pt/C, EtOH) the intermediate amine partially cyclized to the piperidine derivative **2**, via an S_N2 mechanism, with inversion of configuration of the stereogenic center. The reaction was driven to completion by treatment of the mixture with K_2CO_3 in CH_2Cl_2.



Scheme 4. *Reagents and conditions*: (a) $LiAlH_4$, THF, 3 h, rt, 98%; (b) TBDSCl, imidazole, CH_2Cl_2, 3 h, 93%; (c) BMS, 3N NaOH, H_2O_2, 2 h, 65%; (d) pyridine, MsCl, CH_2Cl_2, 12 h, 75%; (e) DMSO, LiN_3, rt, 6 h, 60%; (f) $Pt/C/H_2$ then CH_2Cl_2, K_2CO_3, 55%.

Verification of the *trans* relationship of the H-2 and H-3 of the piperidine ring was established via an ^1H NMR study of the *N*-benzylated derivative of **2**. The *N*-benzyl methylene protons appear as a pair of doublets with a large chemical shift difference, whereas the same signal in the *cis* isomer should appear as a broad singlet.[16] Indicative of the relative position of the three methine protons is that COSY-NMR experiments displayed a splitting of the H-2 resonance only by its adjacent endocyclic methine proton ($J=10.3$ Hz) and that NOESY-NMR showed no interaction between H-2 and H-3.

In conclusion, we have synthesized compound **2**—a key synthetic intermediate for the preparation of (6a*S*,11b*S*,11c*S*) - 1*H* - benzo[*f*]pyrrolo[3,2,1 - *ij*]quinoline (**1**) in nine steps and 7.7% overall yield from **4**.[17] The advantage of the synthetic approach chosen, is the employment of both enantiomers of the chiral auxiliary *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine, used in different stages in the synthesis for the construction of two out of the three stereogenic centers in **2**. The fact that both (2*R*,5*R*) and (2*S*,5*S*) enantiomers of this auxiliary, are readily available by the same synthetic route,[4] makes these compounds attractive agents for the construction of stereogenic centers with highly predictable stereochemistry.

Acknowledgements

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References

1. Katerinopoulos, H. E.; Kouvarakis, A. *Synth. Commun.* **1995**, *25*, 3035–3044.
2. Tagmatarchis, N.; Thermos, K.; Katerinopoulos, H. E. *J. Med. Chem.* **1998**, *41*, 4165–4170.
3. Thermos, K.; Froudakis, G. E.; Tagmatarchis, N.; Katerinopoulos, H. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 883–886.
4. Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298–302.
5. Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, Y. *Tetrahedron Lett.* **1984**, *25*, 857–860.
6. Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236.
7. Evans, D. A.; Ennis, M. D.; Lee, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.
8. *Organic Syntheses*; Wiley & Sons: New York, 1988. Collect. Vol. VI, pp. 897–900.
9. Veldstra, H.; Van De Westeringh, C. *Rec. Trav. Chim.* **1951**, *70*, 1113–1226.
10. Fredga, A.; Westman, L. *Ark. Kemi* **1954**, 193.
11. Fujita, M.; Hiyama, T. *Org. Synth.* **1990**, *69*, 44–54.
12. Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015–6016.

13. Gensler, W. J.; Johnson, F.; Sloan, D. *J. Am. Chem. Soc.* **1960**, *82*, 6074–6079.
14. Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 4643–4646.
15. Myers, A. G.; Cleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488–8489.
16. Walsh, D. A.; Smissman, E. E. *J. Org. Chem.* **1974**, *39*, 3705–3708.
17. Selected spectra: Compound **5**. ^{1}H NMR (250 MHz) δ 1.85–2.14 (m, 6H), 2.41–2.49 (m, 2H), 3.29 (s, 3H), 3.34 (s, 3H), 3.41–3.55 (m, 4H), 3.24–3.3 (m, 1H), 3.69 (dd, $J_1=3$ Hz, $J_2=9.2$ Hz, 1H), 4.01 (ddd, $J_1=7.7$ Hz, $J_2=7.7$ Hz, $J_3=4.2$ Hz, 1H), 4.17–4.23 (m, 1H), 4.46 (d, $J=1$ Hz, 2H), 4.53 (s, 2H), 4.55 (d, $J=7.5$ Hz, 1H), 4.57 (d, $J=7.5$ Hz, 1H), 7.22–7.33 (m, 5H). IR ν (cm^{-1}) 700, 740, 1044, 1110, 1641, 2824–2933. Compound **3**. ^{1}H NMR (300 MHz) δ 1.71–2.04 (m, 2H), 2.42–2.77 (m, 4H), 3.35–3.5 (m, 2H), 3.42 (s, 3H), 3.89 (ddd, $J_1=4.7$ Hz, $J_2=4.7$ Hz, $J_3=8$ Hz, 1H), 4.43 (s, 2H), 4.9 (d, $J=10$ Hz, 1H), 4.99 (d, $J=17$ Hz, 1H), 5.59 (ddt, $J_1=17$ Hz, $J_2=10$ Hz, $J_3=7$ Hz, 1H), 7.17–7.32 (m, 10H). IR ν (cm^{-1}) 701, 739, 1169, 1729, 3500. Compound **2**. ^{1}H NMR (500 MHz) δ 0.0 (s, 6H), 0.89 (s, 9H), 1.5–1.55 (m, 1H), 1.55–1.75 (m, 3H), 1.8–1.87 (m, 2H), 1.94–1.99 (m, 1H), 2.6–2.65 (m, 1H), 2.75 (dt, $J_1=2.6$ Hz, $J_2=11.7$ Hz, 1H), 3.03 (d, $J=10.3$ Hz, 1H), 3.18 (d, $J=11.8$ Hz, 1H), 3.37 (dd, $J_1=7.2$ Hz, $J_2=9$ Hz, 1H), 3.42–3.46 (m, 1H), 3.5 (dd, $J_1=3.9$ Hz, $J_2=10.3$ Hz, 1H), 3.61 (dd, $J_1=5.9$ Hz, $J_2=10.2$ Hz, 1H), 4.38 (d, $J=12$ Hz, 1H), 4.47 (d, $J=12$ Hz, 1H), 7.15–7.35 (m, 10H). ^{13}C NMR (125 MHz) δ 1.0, 18.13, 24.9, 25.9, 25.9, 34.39, 38.07, 46.5, 46.86, 64.53, 65.5, 68.9, 72.6, 126.3, 127.4, 127.6, 127.8, 128.3, 128.5, 138.4.