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Synthesis of enantiomerically pure all *cis*-2,3,6-trisubstituted piperidine: a silicon mediated total synthesis of (+)-carpamic acid

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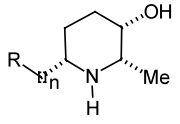
Abstract—A stereoselective total synthesis of (+)-carpamic acid **1** has been achieved from the σ-symmetric 3-[dimethyl(phenyl)silyl]glutaric anhydride **11** featuring its asymmetric desymmetrisation using oxazolidinone **12**. The dimethyl(phenyl)silyl group is not only acting as a masked hydroxy group but also stereodirects ester enolate methylation and facilitates the Curtius reaction of the β-silyl-amide **23**. A highly stereoselective hydrogenation of the imine **10** is the key step in the construction of the all *cis*-2,3,6-trisubstituted piperidine.

Hydroxylated piperidine alkaloids[1] constitute a large family of naturally occurring substances, many of which possess important biological activities.[1e,2] The physiological effects stem from their ability to mimic carbohydrate substrates in a variety of enzymatic processes. Amongst these, the 2,6-disubstituted-3-hydroxypiperidine skeleton with a long aliphatic appendage at the 6-position and all *cis* stereochemistry is present in carpamic acid **1**, azimic acid **2**, spectaline **3**, prosafrinine **4** and cassine **5**. The 2,6-*trans*–2,3-*cis* stereochemistry is found in julifloridine **6** while that in prosopinine **7** and prosopine **8** is found to be 2,6-*trans*–2,3-*trans*. The 2,6-*cis*–2,3-*trans* stereochemistry is present in prosophylline **9**. A number of approaches for racemic and asymmetric syntheses of this class of compounds have appeared.[3]

We propose a potential common intermediate, Δ^1-piperidine **10** for the syntheses of these molecules. A simple catalytic hydrogenation of this would provide the 2,6-*cis* diastereoisomer while sodium cyanoborohydride reduction[4] would preferably give the 2,6-*trans* isomer. The 2,6-*cis*[5] and 2,6-*trans*[6] stereochemistry could also be anticipated by addition of organometallic reagents to the C=N bond of **10** (when $R_2 = H$). There are a number of ways to make the 2,3-*trans* diastereoisomer by inversion[7] at the hydroxy group derivable from the $PhMe_2Si$ functionality.[8] The choice of the silicon group was made as it could provide stereochemical control,[9] viability of reactions impossible with a protected OH group[10] and would facilitate reactions[11] during the various stages of the synthesis.



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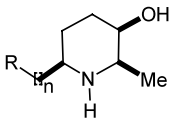
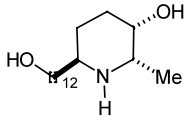
2; n = 5, R = -CO_2H
3; n = 7, R = -$(CH_2)_5COMe$



4; n = 9, R = -COMe
5; n = 10, R = -COMe



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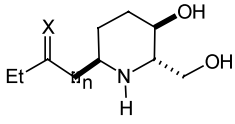
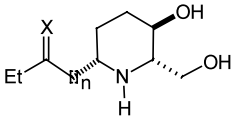


7; n = 9, X = O
8; n = 9, X = H, OH



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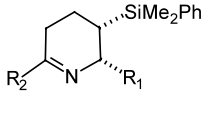

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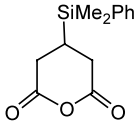

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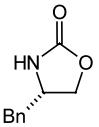

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Keywords: substituted piperidine; carpamic acid; silicon mediated; desymmetrisation; Curtius reaction.

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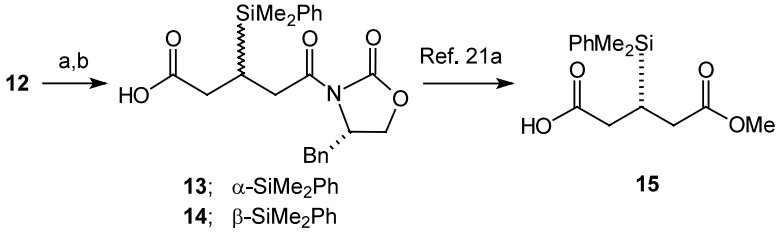
Here we present an enantioselective synthesis of (+)-carpamic acid as a representative example for a general synthetic strategy to all 2,6-dialkyl-3-hydroxypiperidines via the intermediacy of **10**. Carpamic acid **1**, a constituent of an alkaloid, carpaine[12] is isolated from *Carcica papaya*. The plant extract is used in folk medicine[13] and carpaine itself has recently attracted the interest of medicinal chemists.[14] Four racemic synthesis for carpamic acid have been reported.[15–18] The only asymmetric synthesis of (+)-**1** reported, has been from D-glucose.[19] Carpamic acid has also been converted into carpaine.[20]

Our approach to the synthesis of (+)-**1** involved five phases starting from the known anhydride **11**.[21] Of initial importance was the improvement of the diastereoselectivity for desymmetrisation of the anhydride involving our recently developed methodology[22] using oxazolidinone **12**[23] to set the correct stereochemistry at the silicon bearing centre. The resulting mono acid needed homologation to get the desired ketone. The next phases of the synthesis addressed the *anti* selective silicon directed enolate methylation[24] and silicon facilitated Curtius reaction[11] which set the desired stereocentres for OH and Me, and also provided the amino functionality required for the preparation of the Δ^1-piperidine **10**. The fourth stage involved the saturation of the C=N to get all *cis* substituted piperidine. Functional group transformations on the long alkyl chain and conversion of $PhMe_2Si$ group to OH with retention of stereochemistry,[8] completed the synthesis.

We have recently reported[22] a desymmetrisation protocol for prochiral 3-substituted glutaric anhydrides such as **11** using anion of oxazolidinone **12**.[23] The desymmetrisation selectivity was moderate (**13**/**14** = 2/1), but the diastereoisomers were easily separable by fractional crystallization and/or by chromatography of the derived esters. The *tert*-butyl esters of **13** and **14** were converted to the half ester **15** in a convergent fashion (Scheme 1) and used in a total synthesis of a pyrrolidine natural product (+)-preussin.[21] During the present work, the selectivity of desymmetrisation was improved (**13**/**14** = 9/2) using oxazolidinone **12** in the presence of 4-dimethylaminopyridine (DMAP) as an activator in dichloromethane at room temperature (Scheme 2). The mixture of **14** and **15** was converted to a mixture of diazoketones **16** and **17** via their corresponding acid chlorides. After an easy chromatographic separation, the major diazoketone **16** was subjected to Wolff rearrangement[25] to give the benzyl ester **18** in 78% yield. Its hydrogenolysis gave the acid **19** which was converted to a mixed pivaloic anhydride and subsequently reacted with the Grignard reagent derived from 8-benzyloxy-1-bromooctane to furnish ketone **20** in 58% yield (83% based on recovered **19**). The ketone was quantitatively protected as an acetal[26] and the oxazolidinone was removed with $Ti(OEt)_4$ in ethanol to give the ethyl ester **21** in very good yield and 84% recovery of the oxazolidinone **12**.[27] As expected, the α-methylation of **21** took place with high *anti* selectivity[24] (92/8) to give **22** (74%) which was further converted to the primary amide **23** in 85% yield. This, on treatment with $Pb(OAc)_4$/BnOH under modified Curtius reaction conditions,[28] afforded the expected Cbz-protected amine **24** in very good yield. The rearrangement was smooth and was facilitated[11] by the presence of the β-silyl group. The acetal protection was subsequently removed to give the ketone **25** in 65% overall yield from **20**.

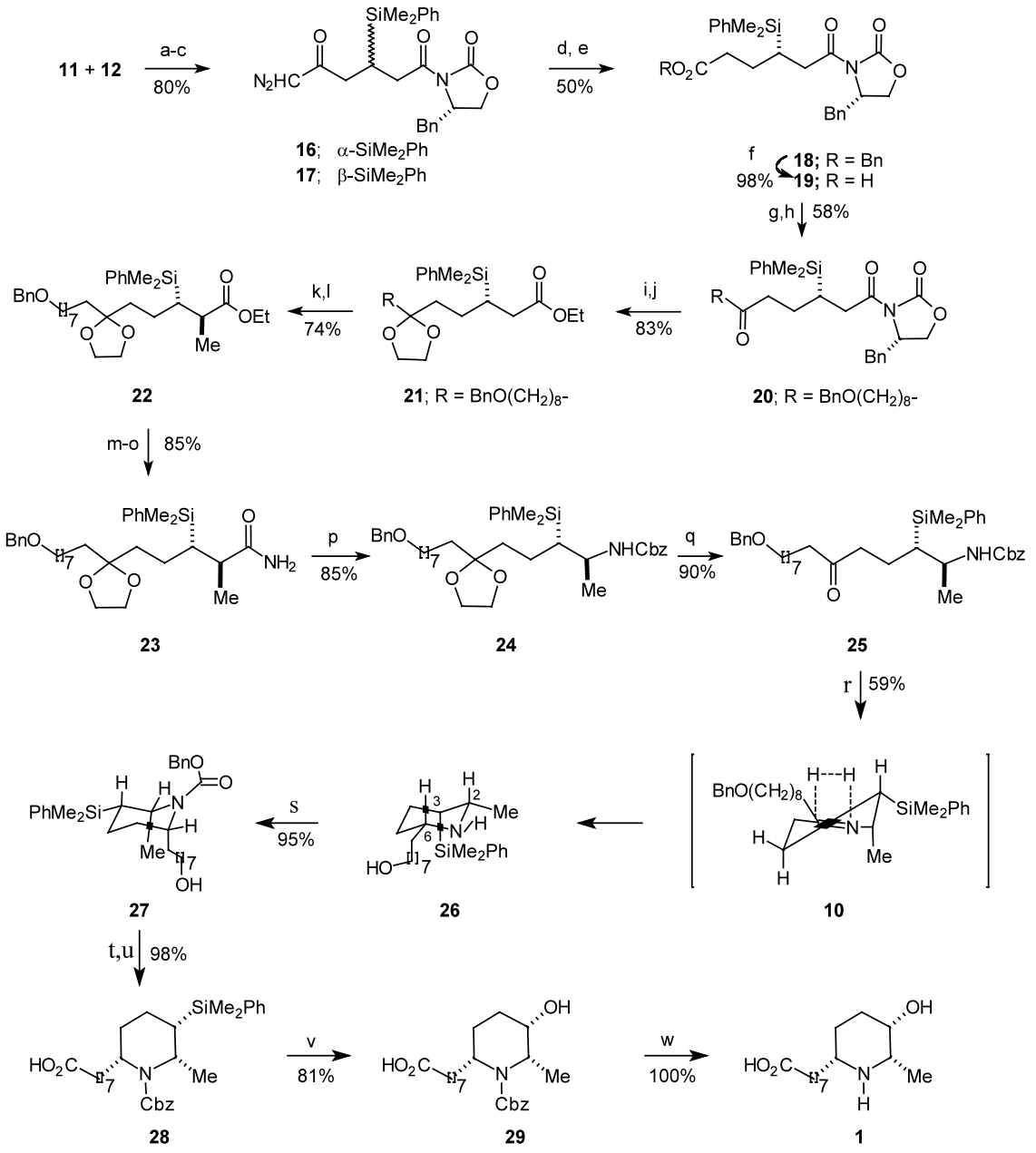
The next important task of the synthesis was Cbz-deprotection of **25** so as to effect the intramolecular amine-ketone condensation to give the intermediate Δ^1-piperidine **10**, followed by a highly stereocontrolled reduction of the imine group. For this, the ketone **25** was subjected to hydrogenolysis which led to removal of the Cbz- group followed by concomitant intramolecular condensation and subsequent hydrogenation of the incipient C=N to give piperidine **26**. The selectivity of imine hydrogenation appeared to be highly solvent dependent.† After much experimentation, the best selectivity (>98%) was achieved by employing 5% acetic acid in toluene giving the desired isomer as its benzyl ether. This upon removal of the benzyl protection by hydrogenolysis in acetic acid, gave the hydroxy amine **26**‡ which was reacted with benzyl chloroformate to give **27**§ (Scheme 2). The *cis* relationship between the



Scheme 1. *Reagents and conditions:* (a) *n*-BuLi, THF, 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU), −78°C; (b) **11**.

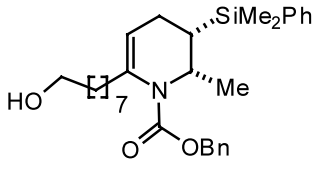
† In 5% acetic acid in ethanol, the ratio (2,6-*cis*/2,6-*trans*) was 82/18 and the 2,6-*trans* isomer was isolated as its *N*-ethyl derivative. *N*-Ethylation during hydrogenation with Pd/C in ethanol has also been reported; see Ref. 29.

‡ During the preparation of **26**, a side product (15%) was also isolated and protected as Cbz-derivative **30**. Data for **30**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.31 (s, 3H), 0.32 (s, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.04–1.80 (m, 14H), 1.80–2.14 (m, 3H), 2.64–2.93 (s, br, 1H), 3.62 (t, J = 6.6 Hz, 2H), 4.65 (dq, J = 6.7, 3.4 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.97–5.12 (m, 1H), 5.23 (d, J = 12.3 Hz, 1H), 7.15–7.30 (m, 8H), 7.40–7.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.26, −4.16, 14.90, 20.88, 25.64, 27.23, 27.87, 29.10, 29.37, 32.71, 35.27, 49.68, 62.96, 67.14, 111.91, 127.81, 127.98, 128.41, 129.10, 133.74, 136.59, 137.34, 153.75; IR (neat) 3438, 1691, 1661, 1250, 1112 cm^{-1}.



Scheme 2. *Reagents and conditions:* (a) DMAP, CH_2Cl_2, rt; (b) $(COCl)_2$, DMF, CH_2Cl_2, rt; (c) CH_2N_2, Et_2O, 0°C; (d) chromatographic separation; (e) $PhCO_2Ag$, BnOH, Et_3N, THF, rt; (f) H_2, Pd–C, EtOAc, rt; (g) Piv-Cl, Et_3N, THF, 0°C; (h) BnO-$(CH_2)_8$-MgBr, THF, −78°C; (i) $(Me_3SiOCH_2)_2$, TMSO–Tf, CH_2Cl_2, −20°C; (j) $Ti(OEt)_4$, EtOH, reflux; (k) Li–TMP, THF, −78°C; (l) MeI, −78 to 0°C; (m) KOH, MeOH, H_2O, reflux; (n) $(Im)_2CO$, CH_2Cl_2, rt; (o) NH_3; (p) $Pb(OAc)_4$, BnOH, DMF, 100°C; (q) TsOH, Me_2CO, H_2O, reflux; (r) H_2 (40–50 psi), Pd–C, AcOH, EtOH or toluene, rt; (s) BnOCOCl, K_2CO_3, THF, rt; (t) $(COCl)_2$, DMSO, Et_3N, −60°C; (u) $KMnO_4$, *t*-BuOH, rt; (v) KBr, AcOOH, rt→40°C; (w) H_2, Pd–C, AcOH, rt.

substituents at 2,6-positions in **26** was confirmed by 2D ROESY experiments, while that between 2,3-substituents (Me and $PhMe_2Si$) from the low $J_{2,3}$ coupling constant (3.4 Hz), typical for the axial–equatorial H-2 and H-3 protons. Hydrogen addition to the cyclic imine **10** from the top face has been proposed to be favoured due to the pseudoaxial positioning of the C-2 methyl substituent and a pseudoequatorial disposition of the bulky dimethyl(phenyl)silyl group at C-3 as depicted in Scheme 2.



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[§] These compounds existed as a mixture of rotamers. This was verified by a temperature dependent NMR study of the benzoate derived from **27** in $C_6D_6/CDCl_3$ (85/15).

Having set the three stereocentres at C-2, C-3 and C-6 correctly, all that remained for the synthesis were conversion of the -CH_2OH to carboxylic acid and silyl function to a hydroxy group. For this, the alcohol **27** was converted to the acid **28**[§] in two steps involving Swern's oxidation to aldehyde followed by $KMnO_4$ oxidation in nearly quantitative yield. Conversion of the silyl group to hydroxy with retention of configuration was achieved using peracetic acid and potassium bromide to give the *N*-Cbz protected carpamic acid **29**[§] in very good yield (81%). This on hydrogenolysis provided (+)-carpamic acid (**1**), mp 228–230°C. Since we started with the homochiral benzyl ester **18**, and the synthetic sequence is not expected to cause any epimerisation, the enantiomeric purity of (+)-carpamic acid should be very high (>99%). This was substantiated by comparison of the specific rotation value ($[\alpha]_D^{21}$ +5.1, *c* 1.38, MeOH) of **1** with those reported[19] and also from the spectroscopic data.[18]

In conclusion, a highly diastereoselective synthesis of (+)-carpamic acid has been achieved from anhydride **11**. The key steps were desymmetrisation of **11** with oxazolidinone **12**, silicon directed highly stereoselective enolate methylation, silicon facilitated Curtius reaction, hydrogenation of **10** which took place with very high selectivity due to the pseudoaxial positioning of the C-2 methyl substituent and a pseudoequatorial disposition of the bulky $PhMe_2Si$ at C-3, and conversion of $PhMe_2Si$ to OH with retention of stereochemistry. As the half ester **15** could be made in an enantioconvergent fashion, both the enantiomers of the natural product could be synthesised by this route.

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