Direct Synthesis of Protected Enantiopure 5-Cyano-3,4-dihydroxypyrrolidin-2-ones from β-Lactam Aldehydes Catalyzed by Iodine

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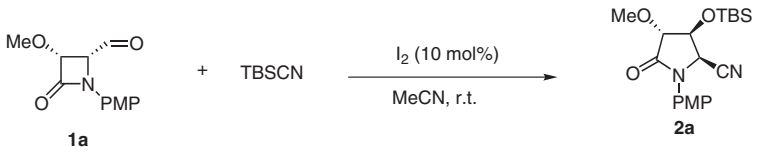
Received 11 June 2008; revised 3 July 2008

Dedicated to Prof. Dr. Carmen Pardo on the occasion of her 65th birthday and retirement

Abstract: A single-step catalytic ring-expansion approach from 4-oxoazetidine-2-carbaldehydes to protected enantiopure 5-cyano-3,4-dihydroxypyrrolidin-2-ones has been achieved by the use of the commercially available and inexpensive reagent, molecular iodine, in the presence of *tert*-butyldimethyl cyanide. Interestingly, the catalyst directs the reaction toward the selective rearrangement reaction of the β-lactam nucleus rather than cyanohydrin formation.

Key words: catalysis, iodine, β-lactams, pyrrolidines, ring expansion



Scheme 1 Preparation of 5-cyanopyrrolidin-2-one **2a**

Introduction

Iminosugars based on polyhydroxylated pyrrolidines have attracted a great deal of attention due to the range of their biological activities, particularly exhibiting action as inhibitors of the enzymes α-galactosidase, α-glucosidase, and glycosidase.[1] Besides, the pyroglutamic acid core has considerable chemical and medicinal importance as it is involved in a wide range of relevant processes.[2]

On the other hand, in addition to the key role that β-lactams have played in medicinal chemistry,[3] the use of 2-azetidinones as chiral building blocks for the synthesis of α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest is now well established.[4] Although many efforts have been made in these fields, the direct preparation of the pyrrolidone core from β-lactam aldehydes was unknown until we merged into this field.[5]

Iodine-mediated reactions have captured much attention recently because of the low cost, ready availability, environmentally benign character, and high tolerance to air and moisture of molecular iodine.[6] Molecular iodine has been identified as a mild catalyst to promote the addition of trimethylsilyl cyanide to ketones as well as for the Strecker reaction.[7] We have recently described the cyanosilylation of 4-oxoazetidine-2-carbaldehydes **1** together with the manipulation of the corresponding β-lactam cyanohydrins.[8] On the basis of these principles, we decided to test the mild Lewis acid nature of iodine for the cyanosilylation of β-lactam aldehydes; however, we obtained instead protected enantiopure 5-cyano-3,4-dihydroxypyrrolidin-2-ones **2** (Scheme 1), which can be regarded as hybrids of the pharmacologically relevant subunits of iminosugar and pyroglutamic acid. Some results of this novel and practical methodology involving a novel C3–C4 bond cleavage of the β-lactam nucleus by using molecular iodine are presented herein.

Scope and Limitations

Among the various solvents and conditions tested, it was found that acetonitrile at room temperature gave the best yields of pyrrolidinone-based products. Protected 5-cyano-3,4-dihydroxy-pyrrolidin-2-ones **2** were efficiently obtained under the optimized conditions: 10 mol% iodine, acetonitrile, 0.3 M solution of β-lactam aldehyde **1**, (1.5–5:1) aldehyde/TBSCN ratio, room temperature (Table 1). Lower catalyst loading slowed the reaction considerably. This transformation tolerates different substituents and functionalities at the 2-azetidinone nitrogen atom, such as aryl (*p*-anisyl, *p*-tolyl, *p*-chlorophenyl), benzyl, allyl, propargyl and methoxycarbonylmethyl moieties. Besides,

SYNTHESIS 2008, No. 17, pp 2835–2839
Advanced online publication: 11.08.2008
DOI: 10.1055/s-2008-1067224; Art ID: Z13708SS

full chirality transfer of the C3 stereogenic centre was observed. Furthermore, at the expense of loss of some diastereoselectivity, sterically encumbered 4-oxoazetidine-2-carbaldehydes **1i** and **1j** were also efficiently converted to the pyrrolidinone derivatives **2i** and **2j** upon iodide catalysis and TBSCN treatment.

Table 1 I_2-Catalyzed Enantioselective Ring Expansion of β-Lactams to γ-Lactams[a]

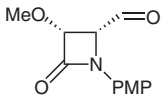
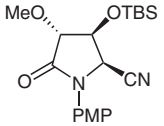
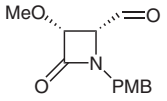
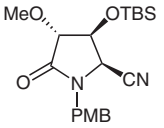
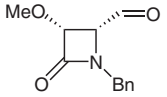
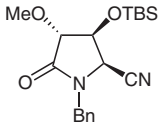
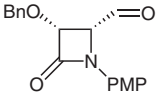
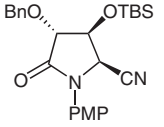
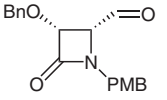
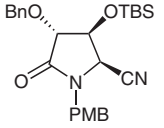
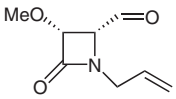
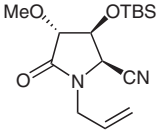
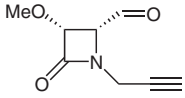
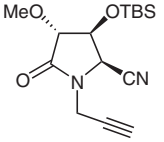
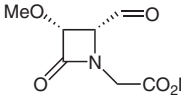
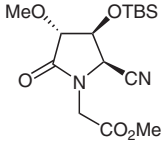
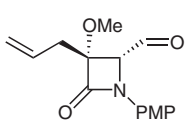
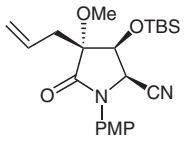
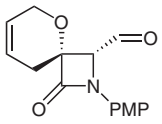
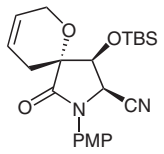
Substrate	Product	Time (h)	Yield (%)[b]
 **1a**	 **2a**	1.5	89
 **1b**	 **2b**	1.5	72[c]
 **1c**	 **2c**	1.5	63[d]
 **1d**	 **2d**	3	54[e]
 **1e**	 **2e**	2.5	54[f]
 **1f**	 **2f**	1.5	56[g]
 **1g**	 **2g**	1	50[h]
 **1h**	 **2h**	1.5	46[i]

Table 1 I_2-Catalyzed Enantioselective Ring Expansion of β-Lactams to γ-Lactams[a] (continued)

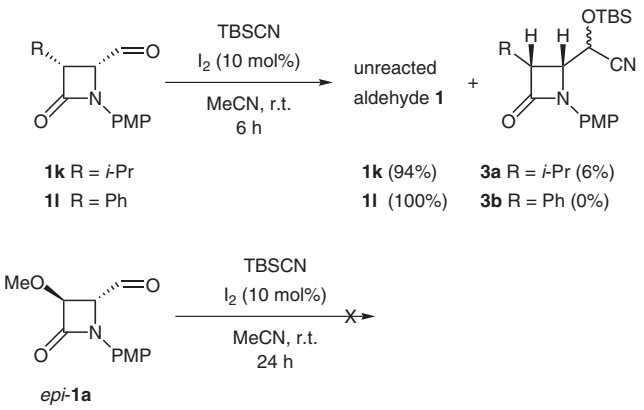
Substrate	Product	Time (h)	Yield (%)[b]
 **1i**	 **2i**	1	50[j]
 **1j**	 **2j**	1	57[k]

[a] PMP = 4-$MeOC_6H_4$; PMB = 4-$MeOC_6H_4CH_2$.
[b] Yield of pure, isolated product with correct analytical and spectral data.
[c] In addition, a further 8% yield of the C5 *anti*-epimer was obtained.
[d] In addition, a further 7% yield of the C5 *anti*-epimer was obtained.
[e] In addition, a further 15% yield of a *syn*/*anti* mixture (73:27) of O-silylated β-lactam cyanohydrin was obtained. TBSCN used: 2 equiv.
[f] In addition, a further 8% yield of the C5 *anti*-epimer was obtained. TBSCN used: 2.5 equiv.
[g] In addition, a further 9% yield of the C5 *anti*-epimer was obtained. TBSCN used: 2.5 equiv.
[h] In addition, a further 7% yield of the C5 *anti*-epimer was obtained. TBSCN used: 4 equiv.
[i] In addition, a further 13% yield of the C5 *anti*-epimer was obtained. TBSCN used: 5 equiv.
[j] In addition, a further 17% yield of the C5 *anti*-epimer was obtained. TBSCN used: 5 equiv.
[k] In addition, a further 18% yield of the C5 *anti*-epimer was obtained. TBSCN used: 5 equiv.

It was desirable to scale the procedure up to obtain gram quantities of pyrrolidinone derivatives. Nicely, it quickly became clear that scale-up was even convenient. Thus, an improved 89% yield of adduct **2a** was obtained when the reaction was carried out on gram scale in comparison with a 78% yield on milligram scale.

The limitations of the method arise from the fact that the ring-expansion reaction is not compatible with C3 substituents at the β-lactam ring different from alkoxy groups (aldehydes **1k** and **1l**, see Scheme 2). When a three-fold excess of TBSCN was used, the starting aldehyde was recovered as the main component together with small amounts of the O-silylated cyanohydrin **3a**. Besides, no reaction was produced under standard reaction conditions starting from the epimeric *trans*-β-lactam aldehyde *epi*-**1a** (*cis*-β-lactam aldehyde **1a** epimerized at C3). From all these results it can be concluded that a *cis*-alkoxy group at the C3 position of the 2-azetidinone ring is required for the ring expansion.

We hope that the basic research work presented herein will be of interest to synthetic chemists, and that it can be applied to the chemical and pharmaceutical industry in the near future.



Scheme 2 β-Lactam aldehydes bearing C3-alkyl, C3-aryl, and *trans*-alkoxy substituents cannot be used in the ring expansion reaction.

^{1}H NMR and ^{13}C NMR spectra were obtained from spectrometers operating at 200 MHz, 300 MHz, or 500 MHz for proton nucleus in $CDCl_3$ solutions, except otherwise stated. ^{1}H chemical shifts are reported in ppm relative to TMS (0.0 ppm) as an internal standard. ^{13}C chemical shifts are reported relative to the central peak of $CDCl_3$ (77.0 ppm). Low- and high-resolution mass spectra were taken on a HP5989A spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Rearrangement Reaction of 4-Oxoazetidine-2-carbaldehyde 1a; Protected 5-Cyano-3,4-dihydroxypyrrolidin-2-one 2a; Typical Procedure

A solution of TBSCN (902 mg, 6.38 mmol) in MeCN (14.3 mL) was added dropwise to a stirred solution of the 4-oxoazetidine-2-carbaldehyde **1a** (1 g, 4.26 mmol) and molecular I_2 (108 mg, 0.426 mmol) in MeCN (14.3 mL) at r.t. under argon. The mixture was stirred for 1.5 h. Then, brine (40 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (5 × 80 mL). The combined organic layers were dried and the solvent was removed under reduced pressure. Chromatography of the residue eluting with hexanes–EtOAc (5:1) gave 1.42 g (89%) of analytically pure **2a** as a colorless oil; $[\alpha]_D^{20}$ +44.9 (*c* 0.7, $CHCl_3$).

IR ($CHCl_3$): 1727 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.19 (s, 3 H), 0.20 (s, 3 H), 0.97 (s, 9 H), 3.75 (s, 3 H), 3.81 (s, 3 H), 4.11 (d, *J* = 7.9 Hz, 1 H), 4.47 (t, *J* = 7.6 Hz, 1 H), 4.68 (d, *J* = 7.3 Hz, 1 H), 6.94 (*AA′*XX′, 2 H), 7.43 (AA′*XX′*, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.1, –4.8, 17.9, 25.5, 53.8, 55.5, 59.7, 71.9, 82.6, 114.6, 115.1, 124.1, 129.3, 158.4, 169.3.

MS (EI): *m*/*z* (%) = 376 (M$^+$, 15), 319 (M – 57, 100), 291 (M – 57 – 28, 98).

Anal. Calcd for $C_{19}H_{28}N_2O_4Si$: C, 60.61; H, 7.50; N, 7.44. Found: C, 60.51; H, 7.42; N, 7.54.

2b

$[\alpha]_D^{20}$ +58.5 (*c* 0.9, $CHCl_3$).

IR ($CHCl_3$): 1719 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 3 H), 0.13 (s, 3 H), 0.92 (s, 9 H), 3.71 (s, 3 H), 3.81 (s, 3 H), 3.92 (d, *J* = 15.0 Hz, 1 H), 3.97 (d, *J* = 7.0 Hz, 1 H), 4.12 (d, *J* = 7.4 Hz, 1 H), 4.20 (t, *J* = 7.1 Hz, 1 H), 5.07 (d, *J* = 14.7 Hz, 1 H), 6.90 (*AA′*XX′, 2 H), 7.20 (AA′*XX′*, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.2, –4.9, 17.8, 25.5, 44.8, 50.7, 55.3, 59.5, 71.6, 82.7, 114.5, 125.7, 130.0, 159.7, 170.0.

MS (EI): *m*/*z* (%) = 390 (M$^+$, 1), 333 (M – 57, 46), 131 (1), 121 (100).

Anal. Calcd for $C_{20}H_{30}N_2O_4Si$: C, 61.51; H, 7.74; N, 7.17. Found: C, 61.63; H, 7.82; N, 7.21.

***anti*-2b**

$[\alpha]_D^{20}$ –9.1 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$): 1721 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 3 H), 0.15 (s, 3 H), 0.87 (s, 9 H), 3.68 (s, 3 H), 3.73 (d, *J* = 5.5 Hz, 1 H), 3.77 (d, *J* = 5.4 Hz, 1 H), 3.81 (s, 3 H), 3.91 (d, *J* = 14.8 Hz, 1 H), 4.43 (t, *J* = 5.4 Hz, 1 H), 5.19 (d, *J* = 14.8 Hz, 1 H), 6.89 (*AA′*XX′, 2 H), 7.22 (AA′*XX′*, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.0, –4.9, 17.8, 25.4, 44.5, 52.1, 55.3, 59.2, 75.1, 83.2, 114.5, 115.5, 126.1, 130.0, 159.7, 169.6.

MS (EI): *m*/*z* (%) = 390 (M$^+$, 1), 333 (M–57, 47), 131 (5), 121 (100).

Anal. Calcd for $C_{20}H_{30}N_2O_4Si$: C, 61.51; H, 7.74; N, 7.17. Found: C, 61.43; H, 7.93; N, 7.02.

2c

$[\alpha]_D^{20}$ +70.2 (*c* 0.5, $CHCl_3$).

IR ($CHCl_3$): 1721 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 3 H), 0.14 (s, 3 H), 0.92 (s, 9 H), 3.72 (s, 3 H), 3.98 (d, *J* = 7.0 Hz, 1 H), 3.99 (d, *J* = 14.6 Hz, 1 H), 4.15 (d, *J* = 7.3 Hz, 1 H), 4.23 (t, *J* = 7.1 Hz, 1 H), 5.14 (d, *J* = 15.0 Hz, 1 H), 7.39–7.26 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.1, –4.9, 17.9, 25.5, 45.4, 51.0, 59.5, 71.6, 82.6, 114.3, 128.5, 128.5, 129.1, 133.8, 170.1.

MS (EI): *m*/*z* (%) = 345 (M$^+$ – 15, 3), 303 (M – 57, 100), 275 (M – 57 – 28, 18), 131 (10), 91 (58).

Anal. Calcd for $C_{19}H_{28}N_2O_3Si$: C, 63.30; H, 7.83; N, 7.77. Found: C, 63.35; H, 7.69; N, 7.58.

***anti*-2c**

$[\alpha]_D^{20}$ –1.8 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 1721 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 3 H), 0.15 (s, 3H), 0.87 (s, 9 H), 3.69 (s, 3 H), 3.76 (d, *J* = 5.5 Hz, 1 H), 3.80 (d, *J* = 5.2 Hz, 1 H), 3.97 (d, *J* = 15.0 Hz, 1 H), 4.44 (t, *J* = 5.4 Hz, 1 H), 5.25 (d, *J* = 15.0 Hz, 1 H), 7.38–7.27 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.0, –4.9, 17.8, 25.4, 45.0, 52.3, 59.2, 75.1, 83.1, 115.4, 128.4, 128.5, 129.1, 134.1, 169.7.

MS (EI): *m*/*z* (%) = 345 (M$^+$ – 15, 4), 303 (M – 57, 100), 275 (M – 57 – 28, 19), 131 (44), 91 (89).

Anal. Calcd for $C_{19}H_{28}N_2O_3Si$: C, 63.30; H, 7.83; N, 7.77. Found: C, 63.21; H, 7.93; N, 7.92.

2d

$[\alpha]_D^{20}$ +62.9 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$): 1727 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 6 H), 0.97 (s, 9 H), 3.83 (s, 3 H), 4.34 (d, *J* = 7.6 Hz, 1 H), 4.55 (t, *J* = 7.3 Hz, 1 H), 4.70 (d, *J* = 7.1 Hz, 1 H), 4.87 (d, *J* = 11.2 Hz, 1 H), 5.19 (d, *J* = 11.2 Hz, 1 H), 6.95 (*AA′*XX′, 2 H), 7.35–7.47 (m, 7 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.0, –4.7, 17.9, 25.5, 54.1, 55.5, 71.9, 73.2, 80.0, 114.7, 115.1, 124.2, 128.1, 128.3, 128.5, 129.3, 137.0, 158.5, 169.5.

MS (EI): *m*/*z* (%) = 452 (M^+, 6), 395 (M – 57, 30), 346 (13), 289 (10), 250 (68), 149 (12), 91 (100).

Anal. Calcd for $C_{25}H_{32}N_2O_4Si$: C, 66.34; H, 7.13; N, 6.19. Found: C, 66.47; H, 7.23; N, 6.35.

2e

$[\alpha]_D^{20}$ +90.4 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 1718 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.10 (s, 3 H), 0.91 (s, 9 H), 3.82 (s, 3 H), 3.94 (d, *J* = 14.6 Hz, 1 H), 4.15 (d, *J* = 7.1 Hz, 1 H), 4.17 (d, *J* = 6.3 Hz, 1 H), 4.28 (t, *J* = 6.7 Hz, 1 H), 4.82 (d, *J* = 11.2 Hz, 1 H), 5.10 (d, *J* = 15.1 Hz, 1 H), 5.16 (d, *J* = 11.2 Hz, 1 H), 6.90 (*AA*′XX′, 2 H), 7.21 (AA′*XX*′, 2 H), 7.34–7.41 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.1, –4.8, 17.9, 25.5, 44.8, 51.0, 55.3, 71.7, 73.0, 80.1, 114.3, 114.5, 125.7, 128.1, 128.3, 128.5, 130.0, 137.0, 159.7, 170.2.

MS (EI): *m*/*z* (%) = 409 (M – 57, 17), 360 (M – 106, 7), 303 (M – 57 – 106, 1), 121 (100), 91 (44).

Anal. Calcd for $C_{26}H_{34}N_2O_4Si$: C, 66.92; H, 7.34; N, 6.00. Found: C, 66.99; H, 7.29; N, 5.97.

***anti*-2e**

$[\alpha]_D^{20}$ +15.0 (*c* 0.6, $CHCl_3$).

IR ($CHCl_3$): 1721 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.84 (s, 9 H), 3.79 (d, *J* = 5.1 Hz, 1 H), 3.82 (s, 3 H), 3.93 (d, *J* = 4.2 Hz, 1 H), 3.95 (d, *J* = 5.4 Hz, 1 H), 4.49 (t, *J* = 5.1 Hz, 1 H), 4.80 (d, *J* = 11.2 Hz, 1 H), 5.13 (d, *J* = 11.5 Hz, 1 H), 5.21 (d, *J* = 14.9 Hz, 1 H), 6.89 (*AA*′XX′, 2 H), 7.23 (AA′*XX*′, 2 H), 7.34–7.40 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.0, –4.9, 17.7, 25.4, 44.5, 52.4, 55.3, 72.7, 75.2, 80.5, 114.5, 115.5, 126.1, 128.0, 128.3, 128.4, 129.9, 136.9, 159.7, 169.8.

MS (EI): *m*/*z* (%) = 409 (M – 57, 3), 360 (M – 106, 11), 303 (M – 57 – 106, 3), 121 (100), 91 (67).

Anal. Calcd for $C_{26}H_{34}N_2O_4Si$: C, 66.92; H, 7.34; N, 6.00. Found: C, 66.83; H, 7.22; N, 6.16.

2f

$[\alpha]_D^{20}$ +77.2 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 1721 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.16 (s, 3 H), 0.17 (s, 3 H), 0.95 (s, 9 H), 3.64 (dd, *J* = 15.1, 7.6 Hz, 1 H), 3.70 (s, 3 H), 3.96 (d, *J* = 6.4 Hz, 1 H), 4.31 (t, *J* = 7.3 Hz, 1 H), 4.37 (d, *J* = 7.1 Hz, 1 H), 4.38 (ddt, *J* = 15.1, 5.0, 1.4 Hz, 1 H), 5.33 (dd, *J* = 16.8, 1.0 Hz, 1 H), 5.35 (dd, *J* = 10.5, 1.0 Hz, 1 H), 5.72 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.1, –4.9, 17.9, 25.5, 44.3, 51.1, 59.5, 71.8, 82.6, 114.5, 120.8, 130.1, 169.9.

MS (EI): *m*/*z* (%) = 295 (M^+ – 15, 4), 253 (M – 57, 100), 225 (M – 57 – 28, 56), 131 (21).

Anal. Calcd for $C_{15}H_{26}N_2O_3Si$: C, 58.03; H, 8.44; N, 9.02. Found: C, 58.12; H, 8.53; N, 8.97.

***anti*-2f**

$[\alpha]_D^{20}$ –3.2 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$): 1722 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 3 H), 0.19 (s, 3 H), 0.92 (s, 9 H), 3.56 (dd, *J* = 15.4, 7.8 Hz, 1 H), 3.66 (s, 3 H), 3.76 (d, *J* = 5.4 Hz, 1 H), 4.04 (d, *J* = 5.4 Hz, 1 H), 4.44 (t, *J* = 5.2 Hz, 1 H), 4.53 (ddt, *J* = 15.4, 4.6, 1.4 Hz, 1 H), 5.33 (d, *J* = 10.5 Hz, 1 H), 5.35 (d, *J* = 17.6 Hz, 1 H), 5.72 (dddd, *J* = 17.6, 9.9, 7.8, 4.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.95, –4.90, 17.8, 25.5, 43.8, 52.7, 59.2, 75.3, 83.1, 115.5, 120.5, 130.1, 169.6.

MS (EI): *m*/*z* (%) = 295 (M^+ – 15, 4), 253 (M – 57, 100), 225 (M – 57 – 28, 53), 131 (61).

Anal. Calcd for $C_{15}H_{26}N_2O_3Si$: C, 58.03; H, 8.44; N, 9.02. Found: C, 57.95; H, 8.57; N, 9.21.

2g

$[\alpha]_D^{20}$ +38.7 (*c* 0.9, $CHCl_3$).

IR ($CHCl_3$): 1726 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 6 H), 0.96 (s, 9 H), 2.38 (t, *J* = 2.6 Hz, 1 H), 3.69 (s, 3 H), 3.83 (dd, *J* = 17.8, 2.4 Hz, 1 H), 3.95 (d, *J* = 7.3 Hz, 1 H), 4.36 (t, *J* = 7.4 Hz, 1 H), 4.62 (d, *J* = 7.3 Hz, 1 H), 4.63 (dd, *J* = 17.6, 2.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.1, –4.9, 17.9, 25.5, 31.2, 50.7, 59.5, 71.9, 74.6, 75.2, 82.3, 114.2, 169.4.

MS (EI): *m*/*z* (%) = 293 (M^+ – 15, 3), 251 (M – 57, 100), 223 (M – 57 – 28, 90), 131 (70).

Anal. Calcd for $C_{15}H_{24}N_2O_3Si$: C, 58.41; H, 7.84; N, 9.08. Found: C, 58.53; H, 8.01; N, 8.99.

***anti*-2g**

$[\alpha]_D^{20}$ +14.4 (*c* 0.6, $CHCl_3$).

IR ($CHCl_3$): 1722 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 3 H), 0.21 (s, 3 H), 0.93 (s, 9 H), 2.36 (t, *J* = 2.6 Hz, 1 H), 3.66 (s, 3 H), 3.74 (dd, *J* = 17.8, 2.4 Hz, 1 H), 3.78 (d, *J* = 5.9 Hz, 1 H), 4.24 (d, *J* = 5.6 Hz, 1 H), 4.47 (t, *J* = 5.7 Hz, 1 H), 4.76 (dd, *J* = 17.7, 2.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.92, –4.89, 17.8, 25.5, 30.8, 52.1, 59.3, 74.2, 75.3, 75.4, 83.0, 115.2, 169.2.

MS (EI): *m*/*z* (%) = 308 (M^+, 1), 293 (M^+ – 15, 22), 251 (M – 57, 100), 223 (M – 57 – 28, 48), 131 (58).

Anal. Calcd for $C_{15}H_{24}N_2O_3Si$: C, 58.41; H, 7.84; N, 9.08. Found: C, 58.33; H, 7.96; N, 9.11.

2h

$[\alpha]_D^{20}$ +20.7 (*c* 0.6, $CHCl_3$)

IR ($CHCl_3$): 1750, 1730 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.17 (s, 6 H), 0.95 (s, 9 H), 3.68 (s, 3 H), 3.73 (m, 1 H), 3.78 (s, 3 H), 3.98 (d, *J* = 7.1 Hz, 1 H), 4.47 (t, *J* = 7.2 Hz, 1 H), 4.62 (d, *J* = 18.1 Hz, 1 H), 4.71 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.1, –4.9, 17.9, 25.5, 42.1, 52.4, 52.6, 59.3, 71.7, 81.9, 114.4, 168.1, 170.4.

MS (EI): *m*/*z* (%) = 285 (M^+ – 57, 100), 257 (M^+ – 57 – 28, 53), 229 (43), 131 (48).

Anal. Calcd for $C_{15}H_{26}N_2O_5Si$: C, 52.61; H, 7.65; N, 8.18. Found: C, 52.93; H, 7.82; N, 7.88.

***anti*-2h**

$[\alpha]_D^{20}$ +10.2 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$): 1750, 1730 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.19 (s, 3 H), 0.20 (s, 3 H), 0.93 (s, 9 H), 3.68 (s, 3 H), 3.73 (m, 1 H), 3.79 (s, 3 H), 3.88 (d, *J* = 6.4 Hz, 1), 4.41 (d, *J* = 6.6 Hz, 1 H), 4.48 (t, *J* = 6.6 Hz, 1 H), 4.68 (d, *J* = 18.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.9, –4.8, 17.8, 25.5, 42.0, 52.6, 52.7, 59.4, 75.7, 82.6, 115.4, 168.1, 170.2.

MS (EI): *m*/*z* (%) = 285 (M^+ – 57, 100), 257 (M^+ – 57 – 28, 73), 229 (37), 131 (35).

Anal. Calcd for $C_{15}H_{26}N_2O_5Si$: C, 52.61; H, 7.65; N, 8.18. Found: C, 52.87; H, 7.31; N, 7.93.

2i

$[\alpha]_D^{20}$ –3.6 (*c* 1.8, $CHCl_3$).

IR ($CHCl_3$): 1719 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.22 (s, 6 H), 1.00 (s, 9 H), 2.68–2.89 (m, 2 H), 3.42 (s, 3 H), 3.82 (s, 3 H), 4.74 (d, *J* = 7.8 Hz, 1 H), 4.84 (d, *J* = 7.6 Hz, 1 H), 5.18–5.28 (m, 2 H), 6.08 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1 H), 6.95 (*AA′*XX′, 2 H), 7.39 (AA′*XX′*, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.7, –4.6, 18.0, 25.6, 34.4, 52.0, 54.4, 55.5, 70.0, 83.1, 114.7, 115.2, 119.2, 125.0, 128.9, 131.5, 158.7, 170.1.

MS (EI): *m*/*z* (%) = 416 (M^+, 27), 359 (M – 57, 75), 332 (M – 57 – 27, 62), 304 (73), 244 (73), 210 (85), 134 (80), 89 (100).

Anal. Calcd for $C_{22}H_{32}N_2O_4Si$: C, 63.43; H, 7.74; N, 6.72. Found: C, 63.52; H, 7.79; N, 6.84.

***anti*-2i**

White solid; mp 108–110 °C (hexanes–EtOAc); $[\alpha]_D^{20}$ +34.4 (*c* 0.8, $CHCl_3$).

IR (KBr): 1719 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.21 (s, 3 H), 0.22 (s, 3 H), 0.95 (s, 9 H), 2.56 (dd, *J* = 14.6, 7.1 Hz, 1 H), 2.79 (dd, *J* = 14.6, 7.1 Hz, 1 H), 3.45 (s, 3 H), 3.83 (s, 3 H), 4.36 (d, *J* = 3.9 Hz, 1 H), 4.60 (d, *J* = 3.9 Hz, 1 H), 5.17–5.31 (m, 2 H), 5.86 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1 H), 6.96 (*AA′*XX′, 2 H), 7.31 (AA′*XX′*, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.8, –4.7, 17.8, 25.6, 32.6, 52.1, 55.5, 56.1, 74.8, 83.4, 114.8, 116.2, 120.0, 125.5, 128.7, 130.8, 158.9, 170.0.

MS (EI): *m*/*z* (%) = 416 (M^+, 55), 359 (M – 57, 41), 327 (M – 57 – 32, 77), 304 (16), 244 (90), 210 (14), 134 (59), 89 (100).

Anal. Calcd for $C_{22}H_{32}N_2O_4Si$: C, 63.43; H, 7.74; N, 6.72. Found: C, 63.32; H, 7.83; N, 6.63.

2j

White solid; mp 106–108 °C (hexanes–EtOAc); $[\alpha]_D^{20}$ +0.7 (*c* 1.0, $CHCl_3$).

IR (KBr): 1721 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 3 H), 0.21 (s, 3 H), 0.98 (s, 9 H), 2.35 (m, 1 H), 2.81 (m, 1 H), 3.82 (s, 3 H), 4.26 (m, 1 H), 4.53 (d, *J* = 7.1 Hz, 1 H), 4.78 (d, *J* = 7.1 Hz, 1 H), 4.83 (m, 1 H), 5.87 (m, 2 H), 6.94 (*AA′*XX′, 2 H), 7.43 (AA′*XX′*, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.9, –4.5, 18.0, 24.2, 25.6, 54.0, 55.5, 63.3, 73.5, 76.3, 114.6, 115.5, 119.8, 124.5, 125.0, 129.3, 158.4, 171.5.

MS (EI): *m*/*z* (%) = 414 (M^+, 29), 386 (M – 28, 100), 357 (M – 57, 67), 329 (M – 57 – 28, 20), 302 (52), 222 (96).

Anal. Calcd for $C_{22}H_{30}N_2O_4Si$: C, 63.74; H, 7.29; N, 6.76. Found: C, 63.79; H, 7.12; N, 6.67.

***anti*-2j**

$[\alpha]_D^{20}$ +11.2 (*c* 1.3, $CHCl_3$).

IR (KBr): 1723 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.18 (s, 3 H), 0.19 (s, 3 H), 0.92 (s, 9 H), 2.40 (m, 2 H), 3.83 (s, 3 H), 4.34 (m, 1 H), 4.34 (d, *J* = 2.2 Hz, 1 H), 4.48 (d, *J* = 2.2 Hz, 1 H), 4.52 (m, 1 H), 5.86 (m, 2 H), 6.96 (*AA′*XX′, 2 H), 7.38 (AA′*XX′*, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.9, –4.9, 17.8, 23.6, 25.5, 55.5, 56.4, 63.1, 74.9, 78.0, 114.7, 115.9, 121.0, 124.8, 125.0, 129.2, 158.6, 170.5.

MS (EI): *m*/*z* (%) = 414 (M^+, 55), 386 (M – 28, 100), 357 (M – 57, 41), 329 (M – 57 – 28, 27), 302 (21), 222 (39).

Anal. Calcd for $C_{22}H_{30}N_2O_4Si$: C, 63.74; H, 7.29; N, 6.76. Found: C, 63.68; H, 7.33; N, 6.89.

Acknowledgment

Support of this work by the DGI-MEC (CTQ2006-10292), Comunidad Autónoma de Madrid (CCG-07-UCM/PPQ-2308), and Universidad Complutense de Madrid (Grant GR74/07) is acknowledged. G.C. thanks the MEC for a predoctoral fellowship.

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