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Enantiopure alkaloid analogues and iminosugars from proline derivatives: stereocontrol in sequential processes

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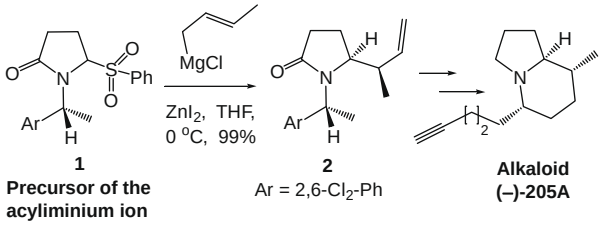
ABSTRACT

An alternative to the use of expensive auxiliaries or catalysts in the synthesis of chiral 2-substituted pyrrolidines is described. Thus, commercial, cheap 4-(*S*)-hydroxyproline was readily transformed into optically pure pyrrolidines, using a one-pot decarboxylation–alkylation reaction as the key step. In this reaction, an acyliminium intermediate was generated, which was trapped by carbon nucleophiles. As postulated by Woerpel, the addition of the nucleophiles to the five-membered ring iminium ions took place stereoselectively, affording 2,4-cis-disubstituted pyrrolidines in high de. The hydroxy group at C-4 can then be removed, or alternatively, it can be used to create new functionalities in the molecule. In this way, optically pure alkaloid analogues and iminosugars were prepared.

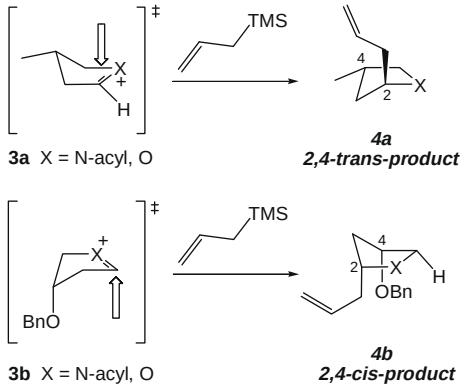
The preparation of optically pure pyrrolidine derivatives has elicited much interest, since these heterocycles are present in many bioactive compounds (such as alkaloids or iminosugars),[1] whose biological activity is often related to the stereochemistry of the product. Among the asymmetric methodologies to prepare substituted pyrrolidines or pyrrolidinones, the addition of nucleophiles to cyclic iminium ions[2] bearing chiral auxiliaries has been a key step in the synthesis of different bioactive compounds [e.g., conversion **1**→**2** (Scheme 1), in the preparation of alkaloid (−)-205A].[3] The use of chiral catalysts instead of chiral auxiliaries avoids the protection–deprotection steps. The appropriate catalysts or auxiliaries could vary for even related substrates.[4]

On the other hand, when five-membered ring iminium or oxonium ions (such as **3a** and **3b**, Scheme 2) present stereogenic centers, the addition of nucleophiles is stereoselective, and the preferred face for the addition depends on the nature of the substituent.[5] Thus, Woerpel postulated that alkyl groups (such as Me) favor an envelop conformation **3a** where the alkyl substituent is equatorial. On the contrary, the alkoxy or acyloxy functions favor an envelop conformation **3b**, with a pseudoaxial OR group, due to stabilizing electrostatic interactions between the oxygen lone electron pairs and the iminium ion.[5b] In both cases, the nucleophile adds from the inner face, to avoid eclipsing interactions on the formation of the product.[6]

Therefore, the intermediate **3a** would yield a 2,4-trans product while the intermediate **3b** would afford a 2,4-cis product.



Scheme 1. Addition of nucleophiles to iminium ions.



Scheme 2. Woerpel's stereoselectivity rules for the addition of nucleophiles to cyclic iminium or oxonium ions.

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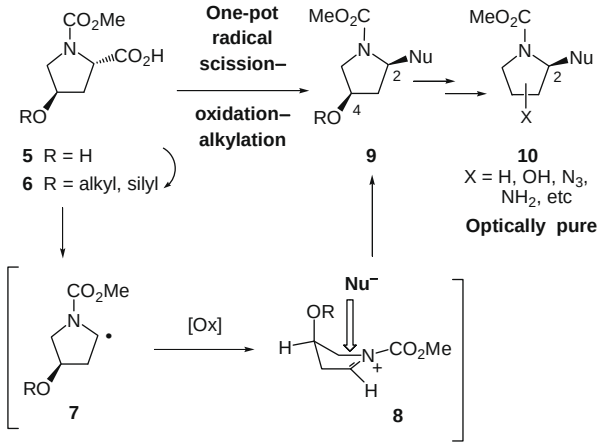
We reasoned that this stereocontrol effect could be used to obtain optically pure pyrrolidines from inexpensive 4-(*S*)-hydroxyproline derivatives (such as the methyl carbamate **5**, Scheme 3), using a sequential process that would couple a decarboxylation to an alkylation reaction. By using sequential processes,[7] the isolation of intermediates is avoided, saving materials and time and reducing the waste. Thus, a more sustainable chemistry is achieved.



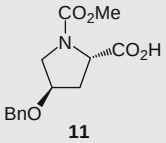
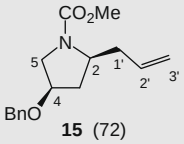
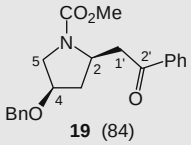
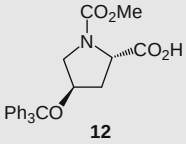
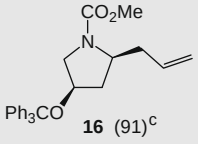
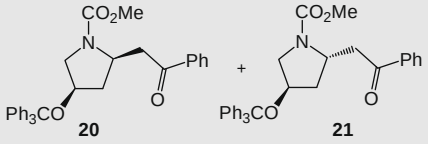
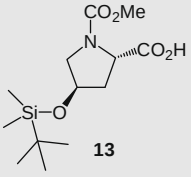
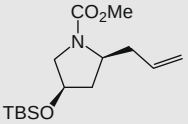
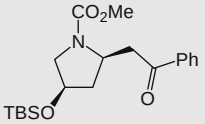
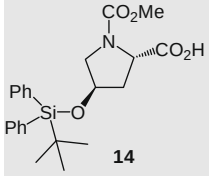
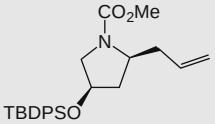
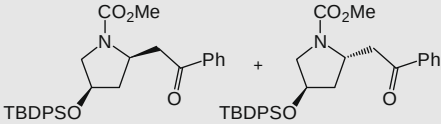
Scheme 3. Stereoselective decarboxylation–oxidation–alkylation.

Our group has developed different sequential processes[8a–c] initiated by radical reactions,[8] and we are currently exploring stereoselective versions of these processes. For instance, we have studied the decarboxylation of proline derivatives where a chiral auxiliary is attached to the nitrogen. However, these auxiliaries are expensive and in many cases the stereoselectivity was not satisfactory.[9] An alternative would be the use of chiral substrates where the stereogenic centers could be later removed or transformed. This Letter explores the feasibility of this approach.

Thus, 4-(*S*)-hydroxyproline **5** was readily converted into ether or silyl ether derivatives **6**, which were treated with (diacetoxyiodo)benzene and iodine under irradiation with visible light (sunlight or commercial lamps).[10] Under these conditions, a radical decarboxylation took place, followed by oxidation of the resulting C-radicals **7** to the acyliminium intermediates **8**, which were trapped by allylsilanes or silyl enolethers. The nucleophiles added preferentially from the inner face of the envelop conformation, affording 2,4-*cis*-pyrrolidines **9**. The OR group at C-4 can be removed or replaced by other functionalities, affording optically pure substituted pyrrolidines **10**.

To study the influence of the protecting group on the yield and stereoselectivity, the hydroxyproline derivatives **11–14** (Table 1) were used as substrates. Their ***R*** groups, which differ in volume, are easily introduced and removed.

Table 1
Stereoselective decarboxylation–oxidation–alkylation

Substrate	Decarboxylation–allylation products, yields[a] (%)	Decarboxylation–alkylation products, yields[b] (%)
 **11**	 **15** (72)	 **19** (84)
 **12**	 **16** (91)[c]	 **20** + **21** **20:21**, 2:1 mixture, 68%[c]
 **13**	 **17** (77)	 **22** (66)
 **14**	 **18** (78)	 **23** (63) + **24** (25)

[a] $PhI(OAc)_2$ (2 equiv) I_2 (0.5 equiv), CH_2Cl_2, *hv*, 3 h; then 0 °C, $BF_3{\cdot}OEt_2$ (2 equiv), allylTMS (3 equiv), 1 h.
[b] PhI(OAc) (2 equiv) I (0.5 equiv), CH_2Cl , *hv*, 3 h; then 0 °C, $BF_3{\cdot}OEt$ (2 equiv), PhC(OTMS)=CH (3 equiv), 1 h.
[c] When substrate **12** was used, the nucleophilic addition was carried out at −50 °C to avoid trityl ether cleavage.

The substrates underwent the scission–alkylation procedure,[11] using allylTMS or silyl enol ethers as nucleophiles, affording 2-allyl derivatives **15–18**[12,13] and 2-acetophenone derivatives **19–24**[12] in good yields (66–91%) and in most cases, high diastereomeric excess. With relatively small-size nucleophiles such as allylTMS, excellent stereoselectivities were observed in all cases. However, with bulkier reagents such as PhC(OTMS)=CH_2 and larger ***R*** protecting groups such as trityl and TBDPS, a mixture of diastereomers was obtained, with the cis isomer as the major one. The attack from the inner face would be less favored due to steric interactions between the protecting group and the nucleophile.

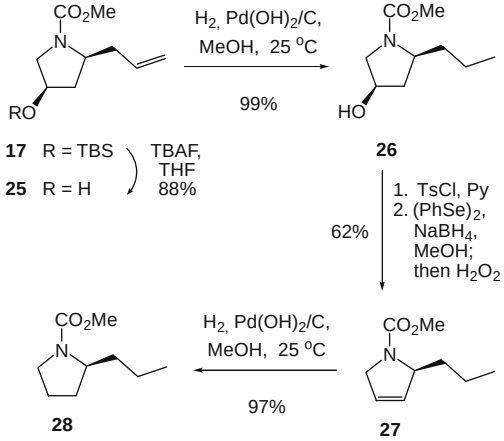
The 2-allyl derivatives **15**–**18** are ring-contracted analogues of the poisonous coniine,[14] while the 2-acetophenone derivatives **19**–**24** are ring-contracted analogues of sedamine.[15] This method would also allow the introduction of other substituents, affording other alkaloid analogues.[1]

After the asymmetric scission–alkylation reaction, the 4-OR group could be deprotected, and the resulting OH was removed by radical deoxygenation, or elimination/reduction, as illustrated with the synthesis of (+)-norconiine methyl carbamate (Scheme 4).[16] Thus, the decarboxylation–allylation product **17** was desilylated to the alcohol **25**, and the lateral chain was reduced, giving compound **26**. The removal of the 4-hydroxy group took place in two steps and afforded the olefin **27** in good overall yield. The latter was hydrogenated, affording the pure (+)-norconiine methyl carbamate **28**.

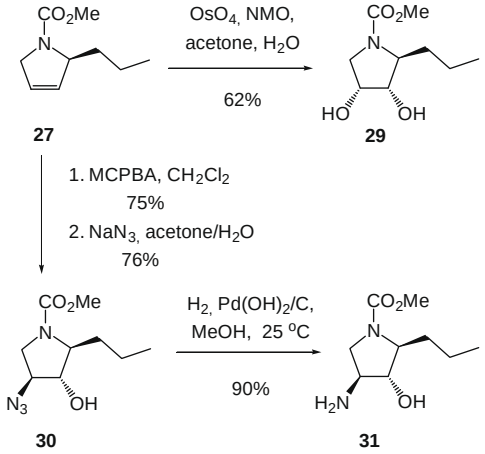
Alternatively, the hydroxy group at C-4 could be used to introduce new functionalities in the molecule. Thus, the elimination product **27** was transformed into iminosugar derivatives **29**–**31** (Scheme 5). Many iminosugars are potent glycosidase inhibitors, and display cytotoxic, antiviral, or hypoglucemic activities.[17] They are also precursors to azanucleosides, which have been used as inhibitors of enzymes, antitumoral agents, etc.[18] As a result, the development of procedures to obtain a variety of azasugars has an ongoing interest.

As shown in Scheme 5, the enantiopure pyrrolidine **27** was readily converted into iminosugar **29** using a dihydroxylation reaction.[19] Also, the epoxidation of substrate **27**, followed by ring opening with sodium azide, generated compound **30**. The azide group was reduced by hydrogenation,[20] yielding the iminosugar **31**.[21] Other functionalities can be introduced using similar strategies.

Since commercial 4-(*S*)-hydroxyproline can be easily transformed into 4-(*R*)-hydroxy, alkoxy or acyloxy derivatives, this methodology would also afford the opposite series of enantiomers.[22] We are currently exploring the stereoselective formation of new alkaloid and iminosugar derivatives, which will be published in due time.



Scheme 4. Synthesis of (+)-norconiine methyl carbamate **28**.



Scheme 5. Stereoselective decarboxylation–oxidation–alkylation.

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References and notes

1. For reviews on natural products containing pyrrolidine rings, see: (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 363–381; (b) Blunt, J. W.; Copp, B. R.; Hu, W. P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2009**, *26*, 170–244; (c) Butler, M. S. *Nat. Prod. Rep.* **2008**, *25*, 475–516; (d) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–165; (e) Jin, Z. *Nat. Prod. Rep.* **2007**, *24*, 886–905; (f) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712; (g) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446; (h) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (i) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964 and references cited therein.
2. (a) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949–3977; (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352; (c) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.
3. (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868–4874; For a recent example using chiral catalysts, see: (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405.
4. For recent reviews on the Mannich reaction and related processes, see: (a) Ferraris, D. *Tetrahedron* **2007**, *63*, 9581–9597; (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569; (c) Schaus, S. E.; Ting, A. *Eur. J. Org. Chem.* **2007**, 5797–5815; (d) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159–186 and references cited therein.
5. (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209; (b) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149–14152; (c) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879–10884; (d) Smith, D.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195–1201; (e) Bonger, K. M.; Wennekes, T.; Filippov, D. V.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2008**, 3678–3688; For similar studies in six-membered-ring oxycarbenium ions, see: (f) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168–169; (g) Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157–1160.
6. The nucleophile adds from the inner face of the envelope, giving the cis product. Attack from this face generates a staggered structure, where the substituents at C-2 and C-3 (or C-5) are not eclipsed. On the contrary, the attack from the outside face is disfavored, due to the eclipsing interactions developed between the substituents at C-2 and C-3 in the transition structure leading to the first-formed trans product.
7. (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581; (c) Nicolaou, K. C.; Edmons, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186; (d) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619–1665 (Part A) and *Tetrahedron* **2006**, *62*, 2143–2173 (Part B) and references cited therein.
8. For recent work on the subject, see: (a) Boto, A.; Gallardo, J. A.; Hernández, D.; Hernández, R. *J. Org. Chem.* **2007**, *72*, 7260–7269; (b) Boto, A.; Hernández, D.; Hernández, R.; Montoya, A.; Suárez, E. *Eur. J. Org. Chem.* **2007**, 325–334; (c) Saavedra, C. J.; Hernández, R.; Boto, A.; Álvarez, E. *Tetrahedron Lett.* **2006**, *47*,

8757–8760. and references cited therein; For related work, see: (d) Díaz-Sánchez, B. R.; Iglesias-Arteaga, M. A.; Melgar-Fernández, R.; Juaristi, E. *J. Org. Chem.* **2007**, *72*, 4822–4825; (e) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. I. *J. Am. Chem. Soc.* **2007**, *129*, 1902–1903. and references cited therein; For a review on the modification of amino acids and carbohydrates through radical chemistry, see: (f) Hansen, S. G.; Skrydstrup, T. *Top. Curr. Chem.* **2006**, *264*, 135–162.

9. Unpublished results on the stereoselective scission–alkylation process using menthyl carbamoyl, camphorsulfonyl, camphanyl, and amino acyl groups as chiral auxiliaries. In many cases, the stereoselectivity was low or moderate. In others, unseparable mixtures of the major and minor diastereomers were formed.
10. Any source of visible light can be used. However, to obtain reproducible results, we carried out the scission with 80-W tungsten-filament lamps, available in DIY shops.
11. *General procedure for the scission–rearrangement process:* To a solution of the hydroxyproline derivative (0.1 mmol) in dry dichloromethane (1.5 mL) were added iodine (13 mg, 0.05 mmol) and DIB (64 mg, 0.2 mmol). The resulting mixture was stirred for 3 h at 26 °C, under irradiation with visible light (80 W tungsten-filament lamp). Then the reaction mixture was cooled to 0 °C (−50 °C when substrate **12** was used) and then $BF_3{\cdot}OEt_2$ (25 μL, 29 mg, 0.2 mmol) and the nucleophile (3 equiv) were added. The mixture was stirred for 1 h; then was poured into 10% aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1:1, 10 mL), and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate mixtures) to give the products.
12. (a) All the products were characterized using NMR, HRMS, and elemental analysis. The proposed stereochemistry was deduced from the value of the ^{1}H NMR coupling constants and it was supported by NOESY experiments. As representative examples, the NMR experiments for the allyl compound **15** and the phenone derivative **19** are described; (b) Product **15**: $[\alpha]_D$ +20.6 (*c* 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$ with TMS, 70 °C) δ_H 1.97 (ddd, *J* = 3.8, 3.8, 13.6 Hz, 3-H_a), 2.05 (ddd, *J* = 6.0, 8.2, 13.6 Hz, 1H, 3-H_b), 2.38 (ddd, *J* = 7.9, 9.1, 13.6 Hz, 1H, 1′-H_a), 2.64 (m, 1H, 1′-H_b), 3.42 (dd, *J* = 3.8, 12 Hz, 1H, 5-H_a), 3.67 (s, 3H, OMe), 3.70 (m, 1H, 5-H_b), 3.90 (m, 1H, 2-H), 4.06 (m, 1H, 4-H), 4.47 (d, *J* = 12.2 Hz, 1H, CH_aPh), 4.50 (d, *J* = 12.6 Hz, 1H, CH_bPh), 5.04 (*J* = 10 Hz, 1H, 3′-Ha), 5.06 (*J* = 17 Hz, 1H, 3′-H_b), 5.75 (m, 1H, 2′-H), 7.26–7.34 (m, 4H, Ph), 7.24 (m, 1H, Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$, 70 °C) δ_C 35.2 (CH_2, 3-C), 38.9 (CH_2, 1′-C), 52.0 (CH_3, OMe), 52.2 (CH_2, 5-C), 56.6 (CH, 2-C), 71.3 (CH_2, CH_2Ph), 77.2 (CH, 4-C), 117.0 (CH_2, 3′-C), 127.5 (2 × CH, Ph), 127.6 (CH, Ph), 128.4 (2 × CH, Ph), 135.2 (CH, 2′-C), 138.3 (C, Ph), 155.4 (C, CO_2). The NOESY experiment showed strong spatial interactions between the benzylic protons (δ_H 4.50/4.47) and the 1′-H_2 (δ_H 2.64/2.38), between the 1′-H_2 and the 3-H_a (δ_H 1.97) and a weaker spatial interaction between 2-H (δ_H 3.90) and 4-H (δ_H 4.06). The ^{1}H NMR coupling constants also showed a cis relationship 2-H/3-H_b/4-H and a trans relationship 2-H/3-H_a and 4-H/3-H_a (J_{3b} = 6.0, 8.2 Hz, while J_{3a} = 3.8, 3.8 Hz); (c) Product **19**: $[\alpha]_D$ +14.1 (*c* 0.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$ with TMS, 70 °C) δ_H 2.13 (br d, *J* = 14.2 Hz, 3-H_a), 2.22 (ddd, *J* = 5.4, 8.2, 14.0 Hz, 1H, 3-H_b), 3.37 (m, 1H, 1′-H_a), 3.64 (m, 2H, 5-H_2), 3.68 (br b, 1H, 1′-H_b), 3.69 (s, 3H, OMe), 4.15 (m, 1H, 4-H), 4.48 (m, 1H, 2-H), 4.51 (s, 2H, CH_2Ph), 7.23–7.31 (m, 5H, Ph), 7.43 (dd, *J* = 7.3, 8.0 Hz, 2H, Ph), 7.52 (dd, *J* = 6.8, 7.2 Hz, Ph), 7.95 (br d, *J* = 7.4 Hz, 2-H, Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$, 70 °C) δ_C 36.2 (CH_2, 3-C), 43.4 (CH_2, 1′-C), 52.0 (CH_3, OMe), 52.4 (CH_2, 5-C), 54.1 (CH, 2-C), 71.0 (CH_2, CH_2Ph), 77.5 (CH, 4-C), 127.5 (2 × CH, Ph), 128.2 (2 × CH, Ph), 128.5 (2 × CH, Ph), 128.6 (3 × CH, Ph), 132.8 (CH, Ph), 137. 4 (C, Ph), 138.0 (C, Ph), 155.2 (C, CO_2), 199.0 (C, 2′-C). As in the previous case, the ^{1}H NMR coupling constants showed a cis relationship 2-H/3-H_b/4-H and a trans relationship 2-H/3-H_a and 4-H/3-H_a (J_{3b} = 5.4, 8.2 Hz, while J_{3a} = 0.0 Hz).
13. (a) Substrate **17** is known: Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704–1710; $[\alpha]_D^{lit}$ +22.9 (*c* 1.4, $CHCl_3$); (b) For compound **17**: $[\alpha]_D^{obs}$ +21.2 (*c* 0.40, $CHCl_3$). (c) As comparison, for compound **23**: $[\alpha]_D$ +13.6 (*c* 0.43, $CHCl_3$), while its epimer **24**: $[\alpha]_D$ −17.3 (*c* 0.45, $CHCl_3$).
14. (a) Passarella, D.; Barilli, A.; Belinghieri, F.; Fassi, P.; Riva, S.; Sacchetti, A.; Silvani, A.; Danieli, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2225–2230; (b) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928.
15. (a) Tirel, P. J.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1989**, *30*, 1947–1950; For a review, see: (b) Bates, R. W.; Kanicha, S. E. *Tetrahedron* **2002**, *58*, 5957–5978.
16. (a) For compound **28** [(+)-norconiine methyl carbamate], $[\alpha]_D$ +26 (*c* 0.3, $CHCl_3$). (b) For a very related compound (the (−)-norconiine *t*-butyl carbamate) see: Blarer, S. J.; Seebach, D. *Chem. Berich.* **1983**, *116*, 2250–2260; $[\alpha]_D$ −34.1 (*c* 1.1, $CHCl_3$).
17. (a) *Iminosugars: from Synthesis to Therapeutic Applications*; Compain, P.; Martin, O.R., Eds.; Wiley-VCH: Chichester, ISBN: 978-0-470-03391-3, 2007.; For pyrrolidine-based iminosugars, see: (b) Doddi, V. R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2007**, 5583–5589; (c) Hakansson, A. E.; van Ameijde, J.; Guglielmini, L.; Horne, G.; Nash, R. J.; Evinson, E. L.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 282–289; (d) Zhou, X.; Liu, W. J.; Ye, J. L.; Huang, P. Q. *Tetrahedron* **2007**, *63*, 6346–6357.
18. For a review article, see: (a) Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541–1554; For articles on the subject: (b) Kočalka, P.; Pohl, R.; Rejman, D.; Rosenberg, I. *Tetrahedron* **2006**, *62*, 5763–5774; (c) Evans, G. B.; Furneaux, R. H.; Hausler, H.; Larsen, J. S.; Tyler, P. C. *J. Org. Chem.* **2004**, *69*, 2217–2220; (d) Kamath, V. P.; Ananth, S.; Bantia, S.; Morris, P. E., Jr. *J. Med. Chem.* **2004**, *47*, 1322–1324; (e) Deng, L.; Scharer, O. D.; Verdine, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 7865–7866; (f) Mayer, A.; Häberli, A.; Leumann, C. J. *Org. Biomol. Chem.* **2005**, *3*, 1653–1658.
19. For related compounds and their uses, see: Murruzzu, C.; Riera, A. *Tetrahedron: Asymmetry* **2007**, *18*, 149–154.
20. Choubdar, N.; Pinto, B. M. *Carbohydr. Res.* **2008**, *343*, 1766–1777.
21. Product **31**: ^{1}H NMR (500 MHz, CD_3OD, 70 °C) δ_H 0.96 (dd, *J* = 7.4, 7.7 Hz, 3′-H_3), 1.39–1.45 (m, 2H, 2′-H_2), 1.69 (m, 1H, 1′-H_a), 1.82 (m, 1H, 1′-H_b), 3.00 (dd, *J* = 7.9, 11.2 Hz, 5-H_a), 3.17 (ddd, *J* = 7.5, 7.5, 7.6 Hz, 4-H), 3.58 (m, 1H, 2-H), 3.69 (s, 3H, OMe), 3.71 (m, 1H, 3-H), 3.88 (dd, *J* = 7.2, 11.2 Hz, 1H, 5-H_b); ^{13}C NMR (125.7 MHz, CD_3OD, 26 °C) Rotamer mixture: δ_C 13.1 (CH_3, 3′-C), 17.8 (CH_2, 2′-C), 33.6/34.5 (CH_2, 1′-C), 50.9/51.6 (CH_3, 5-C), 56.6 (CH, 4-C), 63.9 (CH, 2-C), 80.7/81.4 (CH, 3-C).
22. (a) Kamal, A.; Reddy, D. R.; Reddy, P. S. M. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 803–806; (b) Mandal, A. K.; Hines, J.; Kuramochi, K.; Crews, C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4043–4047; (c) Doi, M.; Nishi, Y.; Kiritoshi, N.; Iwata, T.; Nago, M.; Nakano, H.; Uchiyama, S.; Nakazawa, T.; Wakamiya, T.; Kobayashi, Y. *Tetrahedron* **2002**, *58*, 8453–8459; (d) Gómez-Vidal, J. A.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2481–2484; (e) Bellier, B.; McCort-Tranchepain, I.; Ducos, B.; Danascimento, S.; Meudal, H.; Noble, F.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 3947–3956.