Tetrahedron Letters 53 (2012) 4440–4443

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Convenient strategy for the synthesis of highly functionalizable hydroxylated unsaturated azepanes

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ARTICLE INFO

Article history:
Received 20 April 2012
Revised 5 June 2012
Accepted 11 June 2012
Available online 16 June 2012

Keywords:
Wadsworth–Emmons reaction
Azepane
Carbohydrates
Ring-closing metathesis
Conjugate addition

ABSTRACT

A convenient approach to the construction of dihydroxylated unsaturated azepanes featuring a functional group (ethoxycarbonyl)methyl or (cyano)methyl at C-2 was achieved from a pent-4-enal synthon obtained in four steps from D-xylose. The key step of the sequence relied on the conjugate addition of allylamine to α,β-unsaturated ester or nitrile, prepared by Wadsworth–Emmons olefination. Subsequent RCM afforded the target unsaturated azepanes.

Inhibition of glycosidases has been extensively studied in the last years due to the numerous biochemical roles played by these enzymes. Many natural or synthetic glycosidase inhibitors exhibit interesting therapeutic applications in the treatment of various diseases such as diabetes,[1] viral infection[2] including AIDS,[3] Gaucher's disease,[4] or cancer.[5] Polyhydroxylated pyrrolidines, piperidines, and bicyclic nitrogen-heterocycles such as indolizidines or pyrrolizidines represent the most studied classes of naturally occurring carbohydrate mimics, acting as potent glycosidase inhibitors. A wide synthetic effort devoted to the preparation of these various types of iminosugars has been developed since the pioneering works in the late 1960's.[6]

More recently, polyhydroxylated azepanes have emerged as a new class of iminosugars.[7] After a first synthetic approach by Paulsen in 1967,[8] a set of tri- and tetra-hydroxylated azepanes exhibiting limited inhibition potencies has been prepared by Wong[9] or Depezay.[10] Addition of supplementary substituents on the 7-membered ring afforded inhibitors with micro to nanomolar affinities. Indeed, greater conformational flexibility of the 7-membered ring enables multiple favorable binding interactions in the enzyme active site.[11] Thus, polyhydroxylated azepanes such as **1**–**2** (Fig. 1) featuring an extra hydroxymethyl, carboxyl, or acetamide group have been recently prepared, and might be considered as new potential therapeutic agents.[12–15] Only few general synthetic strategies toward such functionalized polyhydroxyazepanes have been described to date. An important work in this field was developed by Blériot et al. with a method based on the versatile transformation of a key intermediate azacycloheptene **3** produced by ring-closing metathesis (Fig. 1).[12a–d,g]

As a continuation of an ongoing program devoted to the transformation and the valorization of hemicellulose-derived pentoses,[16] we wished to pave the way for a general synthetic route toward functionalized polyhydroxyazepanes, starting from dihydroxylated pent-4-enal **4**, a versatile building-block easily obtained from D-xylose. Thus, we report herein our first efforts toward the preparation of new azacycloheptenes, featuring an unprecedented functional group (ethoxycarbonyl)methyl or (cyano)methyl at the pseudo-anomeric position (Fig. 2). These compounds are precursors of imino C-glycosides, which have become an important class of iminosugars with promising biological and therapeutic properties.[17]

The synthetic sequence began with the preparation of the protected 2,3-dihydroxypent-4-enal **4** from D-xylose (Scheme 1). In our hands, synthesis of the benzyl-protected precursor **5a** according to a previously described procedure[18] was unsatisfactory (35% overall yield). Hence, we turned to the pivaloyl protecting group. Formation of compound **5b** was easily carried out in standard conditions in a 77% overall yield (Scheme 1). Treatment of compound **5b** with activated zinc dust in a 4:1 THF/H_2O mixture under sonication[18,19] gave pent-4-enal **4b** in 80% yield, which was used without further purification.

It is noteworthy that the same sequence could be successfully applied to L-arabinose (the C-4 epimer of D-xylose), the second

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0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.053

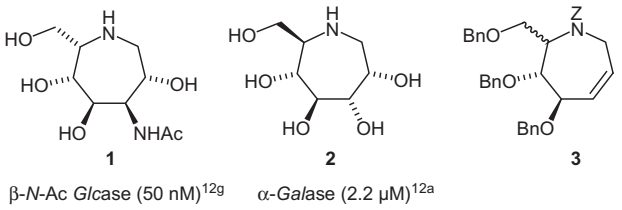


Figure 1. Structures and glycosidase inhibition potencies of polyhydroxylated azepanes previously reported.

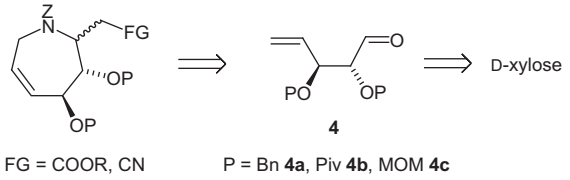
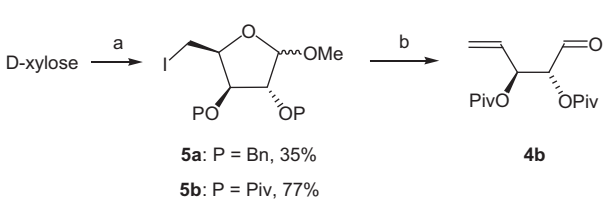


Figure 2. Retrosynthetic scheme toward the target molecules.

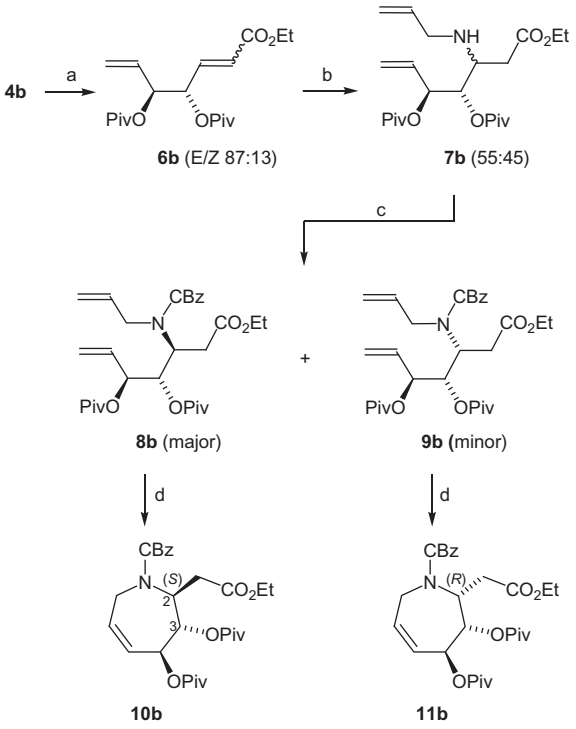
main pentose in the structure of wheat straw and bran hemicelluloses, and to a mixture of both pentoses, yielding **4b** in comparable yields.

First attempts were conducted to prepare the azacycloheptene featuring a (ethoxycarbonyl)methyl group as the functional group. To this aim, aldehyde **4b** was first subjected to a Wadsworth–Emmons olefination with triethyl phosphonoacetate.[20] The reaction was effected at room temperature and yielded efficiently the expected α,β-unsaturated diene **6b** in a 87:13 *E*/*Z* ratio (Scheme 2). Then, aza-Michael addition was carried out under very mild conditions by stirring **6b** with neat allylamine for 16 h at rt, which afforded adducts **7b** in 66% yield (55/45 mixture of diastereomers). Interestingly, in our work, the lack of stereoselectivity might be considered as an opportunity, a source of diastereochemical diversity, to obtain both diastereomers and, after purification and cyclization, epimeric azepanes. It has to be noticed that such an aza-Michael addition was recently reported on analogous substrates,[21] using more restricting conditions with substituted homochiral lithium benzylamides as nucleophiles. This reaction was applied to the synthesis of polyhydroxylated pyrrolidine,[22] piperidine,[23] and pyrrolizidine[24] scaffolds.

Separation of diastereomers was carried out after protection as *N*-benzyloxycarbonyl derivatives **8b** and **9b**.[25] Final ring-closing metathesis with both pure diastereomers to obtain the targeted 7-membered ring compounds proved somewhat sluggish and complete conversion required 72 h of stirring in toluene at 90 °C. Addition of DMSO as scavenger for the ruthenium catalyst and purification by silica gel chromatography afforded β-aminoesters **10b** and **11b** in excellent 83–84% yields.[26] The configuration of



Scheme 1. Synthesis of **4b**. Reagents and conditions: (a) (i) MeOH, HCl (cat.), 12 h then $CaCO_3$, rt, quant.; (ii) TsCl (1 equiv), pyridine, rt, 48 h; (iii) benzyltrichloroacetimidate, triflic acid, dioxane, rt, (40% for the two steps) or Piv-Cl (3 equiv), pyridine, rt, (87% for the 2 steps); (iv) NaI (2 equiv), dimethoxyethane, 48 h, 90 °C, 87% for **5a**, 88% for **5b**; (b) activated Zn dust (10 equiv), THF/H_2O 4:1, 40 °C, sonication, 80%.



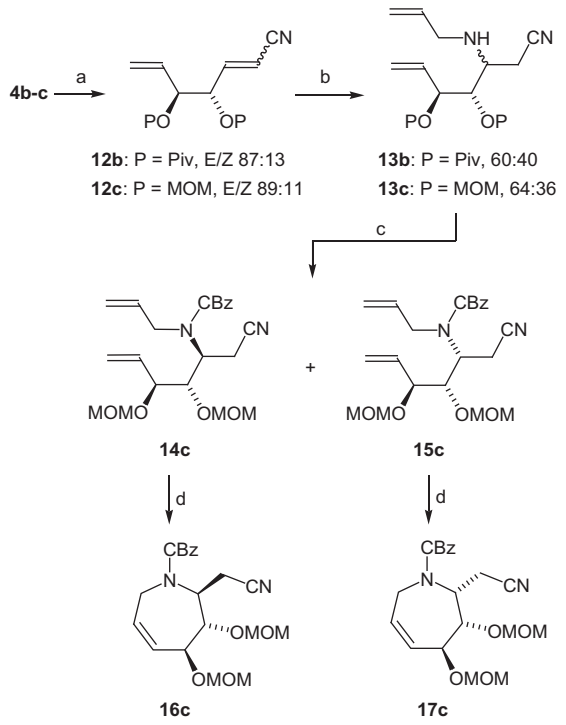
Scheme 2. Synthesis of unsaturated azepanes **10b** and **11b**. Reagents and conditions: (a) $(EtO)_2PO\text{-}CH_2\text{-}COOEt$ (1 equiv), Et_3N (2.1 equiv), LiCl (4 equiv), rt, 5 h, 83%; (b) allylamine (12 equiv), rt, 3 days, 66%; (c) CBz-Cl (2.1 equiv), $NaHCO_3$ (19 equiv), EtOAc/H_2O 1:1, 0 °C 1 h then rt 12 h, 90% (mixture of diastereomers); (d) Grubbs's I catalyst (15 mol %), toluene, 90 °C, 3 days, 83% for **10b**, 84% for **11b**.

the new stereocenter was deduced from NMR analysis of the cyclized compound **10b** derived from the major diastereomer **8b** by comparison of the characteristic $J_{2,3}$ coupling constant ($J_{2,3}$ = 8.8 Hz for both rotamers) indicating a *trans*-configuration as described in the literature for analogous heterocycles (J_{trans} = 8.8–9.4 Hz) and unambiguously confirmed by X-ray crystallography.[12a]

A similar sequence was then applied to the synthesis of a nitrile-functionalized azepane. Reaction of **4b** with diethyl cyanomethylphosphonate was efficiently carried out under the conditions stated above to give α,β-unsaturated nitrile **12b** in a 90% yield and a 87:13 *E*/*Z* ratio. Reaction of **12b** with allylamine afforded the expected Michael adduct **13b** with an unsatisfactory 54% yield in the best conditions (allylamine 4 equiv, methanol, 35 °C), due to the formation of decomposition products.

Altering the protecting groups of the pent-4-enal **4** from pivaloyl **4b** to methoxymethyl (MOM) **4c** permitted to improve this conjugate addition. Hence, the MOM-protected α,β-unsaturated nitrile **12c** was easily obtained in a 68% yield and a 89:11 *E*/*Z* ratio from the known aldehyde **4c**,[27] by condensation with cyanomethylphosphonate. Reaction of **12c** with an excess of allylamine (4 equiv) in methanol at 35 °C afforded the desired β-aminonitrile **13c** in acceptable 76% yield and a 64:36 ratio of diastereomers (de 28%). Again, separation of diastereomers was carried out after protection as *N*-benzyloxycarbonyl derivatives **14c** and **15c**. Terminal RCM was then performed on Cbz-protected compounds to afford target cyanoazaheptenes **16c** and **17c** in 60–80% yields (Scheme 3). The stereochemistry at C-2 for the diastereomers **16c** and **17c** was assigned by analogy with the preceding reaction onto the conjugated ester function.[28]

In conclusion, we have developed a convenient synthetic sequence affording highly functionalizable dihydroxylated unsaturated azepanes featuring (ethoxycarbonyl)methyl or



Scheme 3. Synthesis of unsaturated azepanes **16c** and **17c**. Reagents and conditions: (a) $(EtO)_2PO\text{-}CH_2\text{-}CN$ (1 equiv), Et_3N (2.1 equiv), LiCl (4 equiv), rt, 5 h, 90% for **12b**, 68% for **12c**; (b) allylamine (4 equiv), methanol, 35 °C, 3 days, 54% for **13b**, 76% for **13c**; (c) CBz-Cl (2.1 equiv), $NaHCO_3$ (19 equiv), EtOAc/H_2O 1:1, 0 °C 1 h then rt 12 h, 72% (mixture of diastereomers) for **14c**–**15c**; (d) Grubbs's I catalyst (15 mol %), toluene, 90 °C, 3 days, 80% for **16c**, 60% for **17c**.

(cyano)methyl groups at the pseudo-anomeric position, starting from D-xylose. Introduction of other functional groups such as a phosphonate group at the pseudo-anomeric position to prepare compounds designed as potential inhibitors of glycosyltransferases or glycogen phosphorylase will be undertaken. Further transformations of the double bond by a *syn*- or *anti*-dihydroxylation or aminohydroxylation as well as modification of ester or nitrile group are currently underway to afford a new series of polyhydroxylated azepanes, with the aim of assessing their activities on commercially available glycosidases.

Acknowledgements

This work was supported by the 'Contrat de Plan Etat-Région' (GLYCOVAL, PentoRaf, and PlAneT programs). The authors are grateful to the 'Ministère de l'Enseignement Supérieur et de la Recherche' and FEDER for financial support and a doctoral fellowship (H.T.) and to the 'Fondation du Site Paris-Reims' for a postdoctoral fellowship (S.G.). The authors also warmly thank Dr. D. Harakat and Ms. A. Martinez for ESI-MS and NMR spectra recording and for helpful discussions.

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25. *General procedure for the conjugated addition of allylamine. Preparation of (4S, 5S) ethyl 3-allylamino-N-benzyloxycarbonyl-4,5-bis(pivaloyloxy)hept-6-enoate* (**8b**–**9b**). A solution of allylamine (4 mL, 48 mmol, 12 equiv) and unsaturated ester **6b** (1.6 g, 4 mmol) was stirred at room temperature for 72 h under argon. The reaction was then concentrated in vacuo and the crude mixture was diluted in diethyl ether (20 mL) and washed with 1 M HCl (20 mL) and brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtrated, and concentrated to dryness. The mixture of diastereomers was purified by flash chromatography over silica gel (petroleum ether/diethyl ether 85:15) to afford **7b** as a yellow oil (1.1 g, 66%).
Pure compound **7b** (mixture of diastereomers) (1.0 g, 2.5 mmol) was dissolved in EtOAc/water 1:1 mixture (40 mL) and sodium hydrogenocarbonate (3.95 g, 47.5 mmol, 19 equiv) was added. Benzyl chloroformate (0.74 mL, 5.25 mmol, 2.1 equiv) was then added dropwise and the reaction mixture was kept at room temperature for 12 h. The crude mixture was diluted in EtOAc (50 mL), washed with 1 M HCl (2 × 50 mL) and brine (2 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtrated, and concentrated to dryness. The mixture of diastereomers was purified by flash chromatography over silica gel (petroleum ether/diethyl ether 85:15) to afford pure **8b** (0.66 g, 50%) and pure **9b** (0.54 g, 40%) as yellow oils.
(3S, 4S, 5S) Ethyl 3-allylamino-N-benzyloxycarbonyl-4,5-bis(pivaloyloxy)hept-6-enoate (**8b**). 1:1 Mixture of rotamers; $[\alpha]_D^{19} = -16$ (*c* 0.82, $CHCl_3$); IR (film) ν_{max}

1734, 1499, 1252, 1141 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.37–7.28 (m, 5H), 5.62–5.56 (m, 1H, H–6), 5.39–5.36 (m, 1H, H–5), 5.16–5.10 (m, 6H), 4.05–3.92 (m, 2H, CH_2 ester), 2.69–2.44 (m, 2H, H–2), 1.22–1.16 (m, 21H, CH_3 ester); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 177.2, 170.6, 155.6, 134.7, 132.7, 128.4, 128.2, 127.9, 117.6, 117.2, 72.2, 71.6, 67.4, 60.6, 53.9, 48.5, 41.3, 34.9, 27.1, 14.0; HRMS-(EI) (m/z) $(M+H)^+$ Calcd for $C_{30}H_{44}NO_8$ 546.3067. Found 546.3062. *(3R, 4S, 5S) Ethyl 3-allylamino-N-benzyloxycarbonyl-4,5-bis(pivaloyloxy)hept-6-enoate* (**9b**). 1:1 Mixture of rotamers; $[\alpha]_D^{19} = -14$ (c 0.71, $CHCl_3$); IR (film) ν_{max} 1736, 1481, 1275, 1143 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.37–7.28 (m, 5H), 5.78–5.72 (m, 1H, H–6), 5.22–5.05 (m, 4H), 4.80–4.76 (m, 1H, H–1), 4.07–3.98 (m, 2H, CH_2 ester), 3.86–3.81 (m, 2H), 2.67–2.54 (m, 2H, H–2), 1.24–1.16 (m, 21H, CH_3 ester); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 177.2, 170.5, 156.0, 135.2, 133.7, 128.8, 128.4, 128.2, 118.2, 117.4, 72.2, 72.1, 67.7, 61.3, 54.0, 48.5, 39.3, 35.1, 27.6, 14.5; HRMS-(EI) (m/z) $(M+H)^+$ Calcd for $C_{30}H_{44}NO_8$ 546.3067. Found 546.3062. Anal. Calcd for $C_{30}H_{43}NO_8$: C, 66.03; H, 7.94; N, 2.57. Found: C, 65.83; H, 7.86; N, 2.50.

26. *General procedure for the ring-closing metathesis reaction. Preparation of (3S, 4S) N-benzyloxycarbonyl-5,6-didehydro-2-ethoxycarbonylmethyl-3,4-bis(pivaloyloxy) azepane* (**10b–11b**). Compound **8b** or **9b** (0.54 g, 1 mmol) was dissolved in freshly distilled toluene (150 mL) under argon and degassed over sonication for 1 h. The reaction mixture was heated to 90 °C and Grubbs's I catalyst (20% mol) was added portionwise until the reaction was complete (~48–72 h). DMSO (0.1 mL) was added and the reaction mixture was stirred for 12 h to remove the catalyst. The crude mixture was filtrated and toluene was evaporated in vacuo. The resulting yellow oil was purified by flash chromatography over silica gel (petroleum ether/diethyl ether 3:2) to afford pure **10b** (0.43 g, 83%) or pure **11b** (0.44 g, 84%) as a yellow oil.
(2S, 3S, 4S) N-Benzyloxycarbonyl-5,6-didehydro-2-ethoxycarbonylmethyl-3,4-bis(pivaloyloxy)azepane (**10b**). 1:1 Mixture of rotamers; $[\alpha]_D^{19} = +39$ (c 1.06, $CHCl_3$); IR (film) ν_{max} 3452, 1734, 1481, 1280 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.37–7.28 (m, 5H), 5.73–5.60 (m, 2H, H–6, H–4), 5.41–5.37 (m, 1H, H–5), 5.26–5.13 (m, 2H, CH_2Ph), 5.07 (dd, 0.5H, J = 8.8, 6.3 Hz, H–3), 4.92 (dd, 0.5H, J = 8.8, 4.6 Hz, H–3), 4.85–4.81 (m, 0.5H, H–2), 4.74–4.69 (m, 0.5H, H–2), 4.66–4.61 (m, 0.5H, H–7), 4.46–4.42 (m, 0.5H, H–7), 4.42–4.38 (m, 2H, CH_2 ester), 3.80–3.68 (m, 1H, H–7), 2.87–2.63 (m, 2H, CH_2COO), 1.21–1.16 (m, 21H, CH_3 ester); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 177.2, 170.3, 170.1, 155.9, 136.4, 129.4–127.5 (CH-arom., C–5, C–6), 75.6, 74.7, 70.6, 70.2, 68.2, 67.8, 61.0, 55.4, 55.0, 43.1, 38.9, 38.8, 36.9, 36.1, 27.2, 27.1, 27.0, 14.2; HRMS-(EI) (m/z) $(M+Na)^+$ Calcd for $C_{28}H_{39}NO_8Na$ 540.2573. Found 540.2567. Anal. Calcd for $C_{28}H_{39}NO_8$: C, 64.97; H, 7.59; N, 2.71. Found: C, 64.57; H, 7.68; N, 2.82.
(2R, 3S, 4S) N-Benzyloxycarbonyl-5,6-didehydro-2-ethoxycarbonylmethyl-3,4-bis(pivaloyloxy)azepane (**11b**). 1:1 Mixture of rotamers; $[\alpha]_D^{19} = +20$ (c 1.16, $CHCl_3$); IR (film) ν_{max} 3362, 1734, 1481, 1278 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.38–7.32 (m, 5H), 6.00–5.95 (m, 1H, H–6), 5.75–5.58 (m, 1H, H–5), 5.50 (dd, 1H, J = 7.6, 6.4 Hz, H–4), 5.42–5.31 (m, 1H, H–3), 5.26–4.96 (m, 3H, CH_2Ph, H–2), 4.44 (dd, 0.5H, J = 17.8, 5.5 Hz, H–7), 4.28 (dd, 0.5H, J = 17.8, 6.0 Hz, H–7), 4.12–4.01 (m, 2H, CH_2 ester), 3.86 (dd, 1H, J = 17.8, 6.5 Hz, H–7), 2.77–2.51 (m, 2H, CH_2COO), 1.21–1.16 (m, 21H, CH_3 ester); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 177.5, 177.2, 176.7, 170.3, 170.2, 155.2, 154.8, 136.7, 136.2, 134.0, 133.4, 132.4–127.7 (CH-arom.), 125.1, 124.8, 72.1, 71.9, 69.0, 68.6, 68.0, 67.4, 61.0, 53.4, 52.8, 42.8, 38.9, 38.7, 33.6, 33.5, 27.2, 27.1, 27.0, 14.2; HRMS-(EI) (m/z) $(M+Na)^+$ Calcd for $C_{28}H_{39}NO_8Na$ 540.2573. Found 540.2578.
27. Fourrière, G.; Van Hijfte, N.; Lalot, J.; Dutech, G.; Fragnet, B.; Coadou, G.; Quirion, J.-C.; Leclerc, E. *Tetrahedron* **2010**, *66*, 3963–3972. The authors warmly thank Dr. E. Leclerc for the full details about the experimental procedure.
28. Owing to the complexity of the NMR spectra of both diastereomers **16c** and **17c**, due to the presence of a 50:50 mixture of rotamers, the measurement of vicinal coupling constants proved to be impossible.