Pergamon

Tetrahedron Letters 42 (2001) 7949–7952

TETRAHEDRON LETTERS

A new concise synthesis of nectrisine and its facile conversion to phosphonoazasugars

Michaël Bosco, Philippe Bisseret, Claire Bouix-Peter and Jacques Eustache*

Laboratoire de Chimie Organique et Bioorganique associé au CNRS, Université de Haute-Alsace, Ecole Nationale Supérieure de Chimie de Mulhouse 3, Rue Alfred Werner, F-68093 Mulhouse Cedex, France

Received 14 July 2001; revised 7 September 2001; accepted 10 September 2001

Abstract—The synthesis of new sugar-derived phosphonic acids from protected nectrisine is described. The key step is a highly stereoselective addition of a phosphonate anion to a sugar-derived dihydropyrrole to provide a versatile synthetic intermediate which can be functionalised in multiple ways. © 2001 Elsevier Science Ltd. All rights reserved.

Glycosyltransferases catalyse the transfer of a mono- or oligosaccharide unit from a 'donor' to an 'acceptor' (usually a growing polysaccharide chain). There are several types of donors but they all feature a common core: a sugar 1-phosphate linked either to a nucleotide (NDP sugars) or to a long polyunsaturated alcohol (e.g. undecaprenol). The reaction mechanism is reminiscent of that of glycosidases and is believed to involve a positively charged transition state. For some time, we have been interested in sugar 1-phosphate analogues as inhibitors of glycosyltransferases. In our approach, substitution of the ring oxygen by a nitrogen should strongly favour binding to the enzyme's active site, as observed for glycosidases, while isosteric replacement of the phosphate leaving group by a stable phosphonate should prevent the cleavage to take place. The overall expected result is a strong inhibition of glycosyltransferases.[1,2] In this work, we describe the synthesis of a range of phosphonoazasugars (**2**, **3**, **4**, **5** Fig. 1). In addition the approach was used for a facile preparation of nectrisine (**1** Fig. 1), a known powerful glycosidase inhibitor with immunostimulating properties,[3] which remains an attractive synthetic target.[4]

Hydrazinolysis of phthalimide **6**[5] (Scheme 1) and treatment of the crude amine thus obtained with trifluoroacetic anhydride provided the trifluoroacetamide **7**. Dihydroxylation (OsO_4/NMO) of the olefinic bond and oxidative cleavage ($NaIO_4$) of the resulting diol led to an aldehyde which cyclised to the protected aminal **8** upon standing. Initial attempts to remove the benzyl groups in **8** by hydrogenolysis, using a variety of conditions, were disappointing as the desired deprotected product **10** was obtained only in low yield, always accompanied by substantial amounts of the amino-alcohol arising from reduction of the latent aldehyde function in **8**. Fortunately, and to our surprise in view of the expected sensitivity of compounds **8** and **9**, the desired conversion could be effected in high yield by BCl_3 treatment at low temperature.[6] Hydrolysis of the trifluoroacetamide with dilute NaOH and concomitant dehydration, followed by ion-exchange chromatography (Sephadex® CM-C-25 (NH_4^+), elution with 2% aqueous ammonia) completed our synthesis of nectrisine, thus obtained in nine steps and 18% overall yield starting from commercially available 2,3,5-tri-*O*-

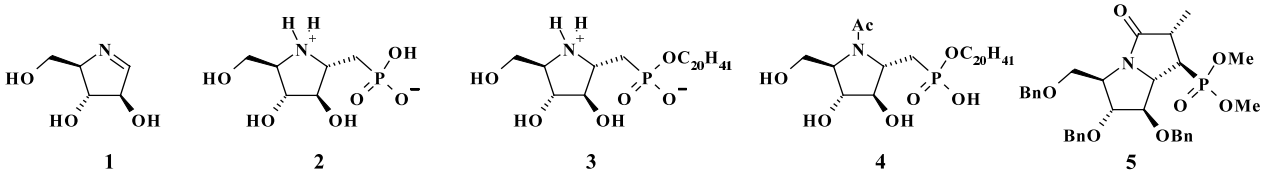
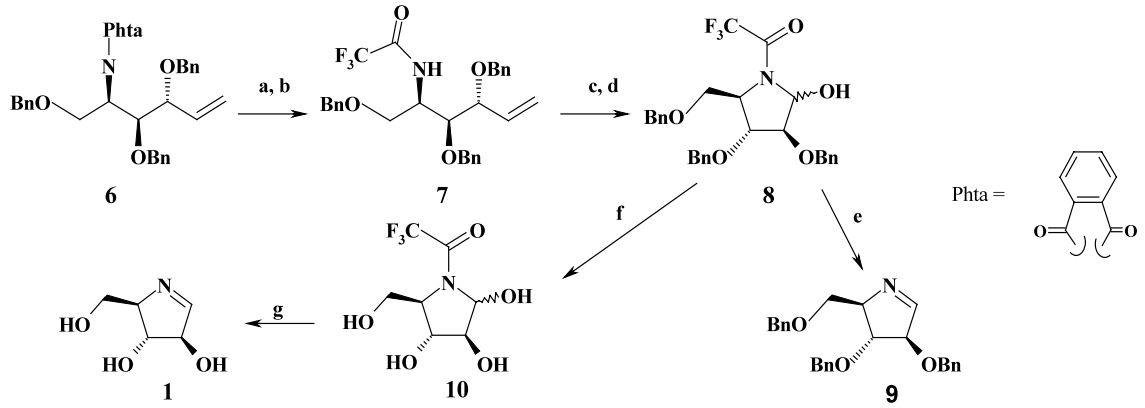


Figure 1.

* Corresponding author. Fax: 33 (0)3 89 336860; e-mail: j.eustache@uha-mulhouse.fr

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)01684-7

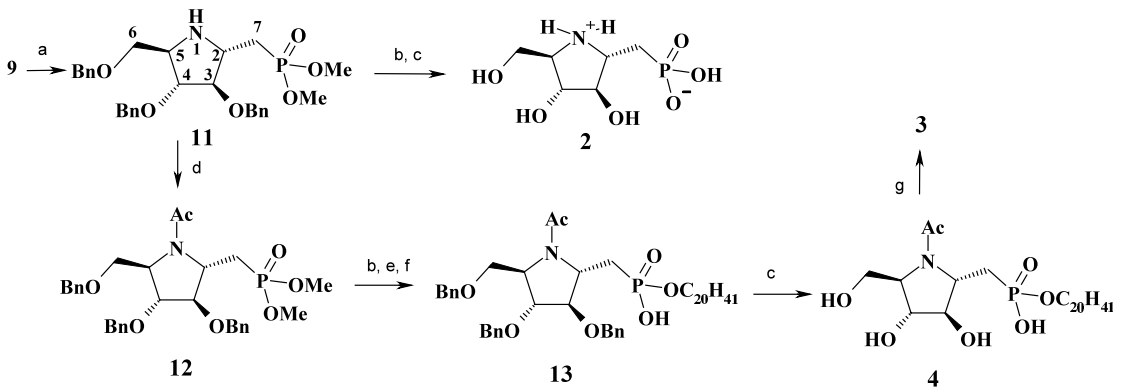


Scheme 1. (a) $N_2H_4{\cdot}H_2O$, ethanol, reflux, 1.5 h; (b) $(CF_3C{=}O)_2O$, NEt_3, 0°C–rt, 2 h, 72% (two steps); (c) OsO_4 (cat.), NMO, THF/acetone/H_2O 4/4/1, rt, 48 h; (d) $NaIO_4$, THF/acetone/H_2O (4/4/1), rt, 1.5 h, 98% (two steps); (e) LiOH (0.5 M) in THF/MeOH/H_2O (4/4/1), rt, 2 h, 86%; (f) BCl_3, CH_2Cl_2, −78°C, 2 h, then −40°C, 16 h, 96%; (g) NaOH (0.5 M), rt, 30 min, then AcOH to pH 4, 96%.

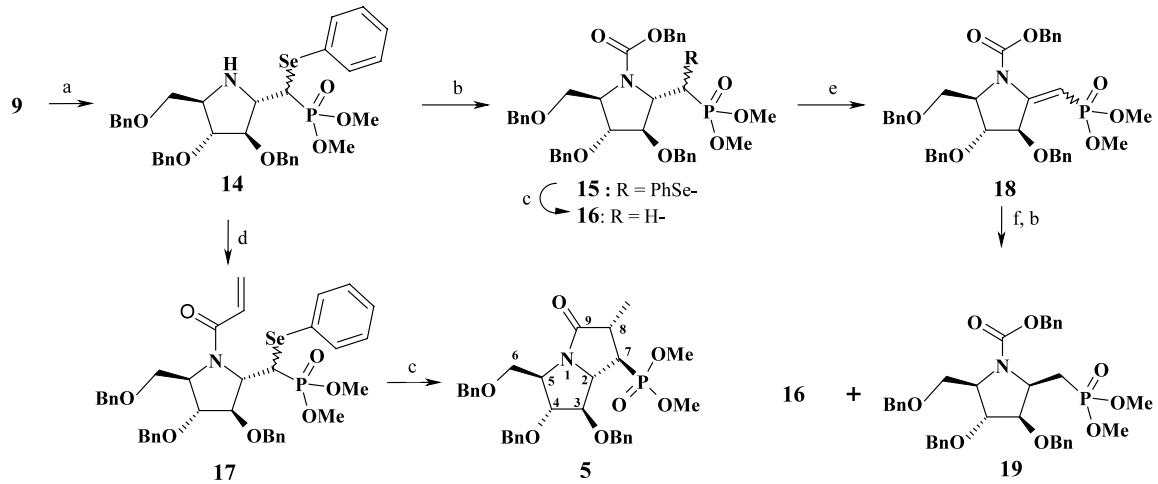
benzyl-(D)-arabinose.[5] This synthesis compares well with previously published ones.[4]

The use of protected nectrisine **9** for the synthesis of 2-phosphonylmethylpyrrolidines (Scheme 2) was explored next. Although additions of alkyl or aryl lithium or Grignard reagents to simple cyclic imines are known, the use of the method with more complex, sugar-derived dihydropyrroles seems to have been reported only twice.[7] Furthermore, addition of phosphonate anions even to simple imines was, to the best of our knowledge, unprecedented. We found that treatment of **9** with lithiated dimethylmethylphosphonate, under Lewis acid catalysis afforded exclusively the substituted 2-(*S*)-pyrrolidine **11** albeit in modest yield.[8] Our synthesis was then completed as shown in Scheme 2: selective cleavage of the phosphonate esters with TMSBr and removal of the benzyl protective groups with BCl_3 afforded cleanly the free phosphonate **2**, the first example of a free azasugar-derived phosphonic acid. Coupling of this phosphonic acid with long chain alcohols was then attempted. Among the various methods tested, only Vasella's method worked well.[9] Thus, *N*-acetylation of **11** was followed by cleavage of the phosphonate esters and conversion of the resulting phosphonic acid to the corresponding triethylammonium salt. Treatment with trichloroacetonitrile then 1-eicosanol afforded the corresponding monophosphonate in good yield. Cleavage of the benzyl protecting groups gave the free *N*-acetyl phosphonate **4** and *N*-deacetylation by acidic treatment gave **3**.

We examined whether the highly stereoselective addition of simple dimethyl methylphosphonate to the iminosugar **9**, could be extended to more complex phosphonates. Our intention was to exploit the resulting intermediates for further derivatisation and we decided to focus on α-selenophosphonates because of their high synthetic potential. We were pleased to find that treatment of the cyclic imine **9** with lithiated dimethylphenylselanylmethylphosphonate **20**[10] afforded exclusively **14**, having the α-configuration, as a ca. 1:1 mixture of 7(*R*) and 7(*S*) isomers, in good yield. The corresponding Cbz derivatives 7(*R*) **15** (48%) and 7(*S*) **15** (46%) could be separated by chromatography. Treatment with triphenyltin hydride effected clean removal of the phenylselanyl group to afford in both cases **16** quantitatively.[11] On the other hand, treatment of **14** with acryloyl chloride provided the acrylamide **17** which, upon treatment with triphenyltin hydride, was



Scheme 2. $LiCH_2P(O)(OMe)_2$ (2 equiv.), $BF_3{\cdot}OEt_2$, THF, −78°C, 2 h, rt, 32%; (b) TMSBr, CH_2Cl_2, 0°C–rt, 16 h; (c) BCl_3, CH_2Cl_2, −78 to −40°C, 97% (**2**), 90% (**3**); (d) Ac_2O, pyridine, 20°C, 16 h, 61%; (e) NEt_3, MeOH, rt, 10 min; (f) $C_{20}H_{41}OH$, CCl_3CN, pyridine, 70°C, 16 h, 76%; (g) 8N HCl, 45°C, 16 h, 40%.



Scheme 3. (a) LiCH(PhSe)P(O)(OMe)$_2$ (2 equiv.), $BF_3{\cdot}OEt_2$, THF, −78°C, 2 h, rt, 69%; (b) CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, 20°C, 1.5 h, 48%; (c) Ph_3SnH, toluene, 110°C, 16 h, 80% (**16**) or 37% (**5**); (d) CH_2=CH–COCl, NEt_3, 20°C, CH_2Cl_2, 0°C, 2 h, 64%; (e) *m*CPBA (2 equiv.), CH_2Cl_2, 4°C, 16 h, 64% (from **15** (*R*)), 66% (from **15** (*S*)); (f) H_2 (P=8 bar), Pd/C 10%, MeOH, 16 h.

converted to the protected cyclic phosphonate **5**, obtained as a single isomer to which we tentatively attribute the structure indicated in Scheme 3. This provides a convenient entry toward cyclic, conformationnaly constrained phosphonoazasugars.

Finally, all phosphonoazasugars described so far have the 2-α configuration, but we are also interested in 2-β analogues and we were intrigued by the possibility of inverting the configuration at C-2 in **15** (from α to β), again using selenium chemistry. Our approach is shown in Scheme 3. There were no previous reports of selenenic acid eliminations in β-amino-(or β-amido)-selenoxides to afford enamines. In our case, the method proved to be highly effective: thus, 7(*R*) **15** and 7(*S*) **15** were submitted to a selenide oxidation/selenenic acid elimination sequence. The faster (presumably 7(*S*)) migrating isomer gave exclusively *Z*-**18** as evidenced by the strong NOE between protons 7 and 3 (see Scheme 3 for numbering), while the other (presumably 7(*R*)) isomer gave **18** as an *E*/*Z* mixture.[12] To complete the synthesis, catalytic hydrogenolysis of the Cbz group and simultaneous hydrogenation of the double bond in **18** was performed. The *Z* and *E* isomers of **18** were separated by chromatography and submitted to the same catalytic hydrogenation conditions. In both cases, **16** was formed predominantly: the major, *Z*-**18** isomer afforded a 6:4 mixture of α-(**16**) and β-(**19**) anomers in 76% yield, and the minor, *E*-**18** isomer afforded 71% of an anomeric mixture containing less than 10% of **19**.

Thus, starting from **6**, obtained in a few steps from commercially available 2,3,5-tri-*O*-benzyl-arabinose, we have devised a short synthetic route to nectrisine as well as to a range of 2-phosphonylmethyl-polyhydroxy-pyrrolidines (phosphonoazasugars). Phosphonoazasugars are analogues of sugar 1-phosphates, a class of compounds involved in many important biochemical processes. In particular the new phosphonates **2**–**4** are candidates as inhibitors of mycobacterial glycosyltransferases. Exploration of the potential of the selenium chemistry briefly examined here, in particular for the synthesis of rigid analogues of the phosphonosugars described in this work, is in progress.

Acknowledgements

We thank Drs. Didier Le Nouen and Stéphane Bourg for help with NMR recording and spectra interpretation. We gratefully acknowledge the French Ministry of Research and the 'Fondation de l'Ecole Nationale Supérieure de Chimie de Mulhouse' for fellowships to M.B and C.B.-P., respectively. This work was done within the frame of a COST program (action D13 New Molecules for Human Health).

References

1. (a) Casero, F.; Cipolla, L.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1996**, *61*, 3428–3432; (b) Cipolla, L.; La Ferla, B.; Nicotra, F.; Panza, L. *Tetrahedron Lett.* **1997**, *38*, 5567–5568.
2. Vaghefi, M. M.; Bernacki, R. J.; Dalley, N. K.; Wilson, B. E.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1383–1391.
3. Shibata, T.; Nakayama, O.; Tsurumi, Y.; Okuhara, M.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *51*, 297–301.
4. (a) Kayariki, H.; Takase, S.; Setoi, H.; Ucida, I.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 1725–1728; (b) Chen, S.-H.; Danishevsky, S. J. *Tetrahedron Lett.* **1990**, *31*, 2229–2232; (c) Kayariki, H.; Nakamura, K.; Takase, S.; Setoi, H.; Uchida, I.; Terano, H.; Hashimoto, M.; Tada, T.; Koda, S. *Chem. Pharm. Bull.* **1991**, *39*, 2807–2812; (d) Kim, Y. J.; Kitahara, T. *Tetrahedron Lett.* **1997**, *38*, 3423–3426; (e) Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron* **1999**, *55*, 8353–8364.
5. Bouix, C.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **1998**, *39*, 825–828.

6. Congreve, M. S.; Davison, E. C.; Fuhry, M.-A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663.
7. (a) Furneaux, R. H.; Limberg, G.; Tyler, P. C.; Schramm, V. L. *Tetrahedron* **1997**, *53*, 2915–2930; (b) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34*, 7213–7216.
8. In related examples, using simpler aryllithiums, additions to cyclic imines appear to proceed in modest to medium yields: Mutzer, J.; Meier, A.; Buschmann, J.; Luger, P. *Synthesis* **1996**, 123–132 and Ref. 7.
9. Billault, I.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 1137–1149.
10. **20** is best prepared in good yield (64%) from readily available dimethylmethylphosphonate by lithiation (*n*-BuLi), transmetallation using $ZnCl_2$ and treatment by phenylselenenyl chloride. All experiments were performed at −78°C. Under these conditions, no bis selenylation was observed.
11. All new compounds show HRMS data in agreement with the expected structure. The α configuration in **16** was deduced from NMR data: protons H-3 and H-4 appear as singlets, indicating and all *trans* relationship for protons H-2, H-3, H-4, H-5. This was further ascertained by comparing ROESY data for the *N*-PMB derivatives corresponding to **16** and **19** (the presence of rotamers precludes direct ROESY analysis of **16** and **19**). Notable features include: for the '**19**-derived PMB', strong 'through space' interactions between H-2 and H-3/H-5, which are absent in the other PMB derivative. The positive NOE effect between protons 3 and 7 in **5** is indicative of an *exo* location for the phosphonate group. NMR data for selected compounds are listed below:
16: ^{1}H NMR (400 MHz, 393 K, $C_2D_2Cl_4$) δ 2.34 (1H, dt, J=15, 15, 11 Hz, H-7), 2.6 (1H, broad, H′-7), 3.60–3.71 (7H, m, H-6+2×OCH_3), 3.96 (1H, broad, H′-6), 4.22 (1H, dd, J=10, 6 Hz, H-5), 4.25 (1H, s, H-3 or H-4), 4.30 (1H, ddd, J=10.8, 6, 2.4 Hz, H-2), 4.42 (1H, s, H-4 or H-3), 4.47 (1H, d (ABq), J=12 Hz, -OCH_aH_bPh), 4.45–4.65 (5H,-overlapping Abq's, -OCH_2Ph), 5.15 (1H, d (ABq), J=12 Hz, -C(=O)OCH_aH_bPh), 5.24 (1H, d (ABq), J=12 Hz, -C(=O)OCH_aH_bPh), 7.3–7.4 (20H, m, Ph).
1: ^{1}H NMR (250 MHz, 300 K, D_2O) δ 3.79 (1H, dd, J=9.4, 3.6 Hz, H-6), 3.90 (1H, m, H-5), 3.97 (1H, dd, J=9.4, 3.7 Hz, H′-6), 4.12 (1H, t, J=5.3 Hz, H-4), 4.78 (1H, t, J=5.3 Hz, H-3), 7.73 (1H, broad s, H-2).
2: ^{1}H NMR (250 MHz, 300 K, D_2O) δ 1.98 (2H, dd, J=17.2, 7.3 Hz, H-1+H′-1), 3.52 (1H, m, H-5), 3.59 (1H, m, H-2), 3.79 (1H, dd, J=12.6, 6.2 Hz, H-6), 3.90 (1H, dd, J=12.6, 3.9 Hz, H′-6), 3.95–4.05 (2H, m, H-3+H-4). ^{13}C NMR (62.9 MHz, 300 K, D_2O) δ 29.19 (J=131 Hz, C-7), 58.84, 59.99 (J=2 Hz, C-2), 63.14, 74.90, 76.02 (J=8.5 Hz, C-3). ^{31}P NMR (101.2 MHz, 300 K, D_2O) δ 16.66 (s).
3: ^{1}H NMR (250 MHz, 300 K, CD_3OD) δ 0.89 (3H, t, J=6.8 Hz, CH_3), 1.27 (34H, m, -CH_2-), 1.63 (2H, m, -O-CH_2-CH_2-), 2.01 (1H, ddd, J=17, 14, 7.8 Hz, H-7), 2.10 (1H, ddd, J=17.6, 14, 6.5 Hz, H′-7), 3.48 (1H, m, H-5), 3.59 (1H, m, H-2), 3.75 (1H, dd, J=11.7, 7 Hz, H-6), 3.83–4.0 (4H, m, H-4+H′-6+-O-CH_2), 4.0 (1H, m, H-3). ^{13}C NMR (62.9 MHz, 300 K, CD_3OD) δ 14.49, 23.78, 26.95, 27.67 (J=132 Hz, C-7), 30.53, 30.82, 32.08 (J=6.5 Hz, -O-CH_2-CH_2-), 33.12, 60.15, 61.29 (J<1 Hz, C-2), 65.79 (J=6 Hz, -O-CH_2-CH_2-), 65.90, 76.96, 80.55 (J=8 Hz, C-3). ^{31}P NMR (101.2 MHz, 300 K, CD_3OD) δ 19.72 (s).
4: ^{1}H NMR (400 MHz, 300 K, CD_3OD) (~2:1 mixture of rotamers. Signals which could be attributed to major and minor rotamers are listed as 'M' and 'm', respectively) δ 0.88 (M) (3H, t, J=6.9 Hz, CH_3), 1.19–1.43 (34H, m, -CH_2-), 1.61 (2H, m, -O-CH_2-CH_2-), 1.80 (M) (~0.66H, ddd, J=17.3, 15.2, 1.9 Hz, H-7), 1.93 (m) (~0.33H, m, H-7), 2.11(m) (~1H, s, -C(O)-CH_3), 2.13 (M) (~2H, s, -C(O)-CH_3), 2.50 (M) (~0.66H, dt, J=15.5, 12.1 Hz, H′-7), 3.67(m) (0.33H, m, H-6), 3.79 (M) (~0.66H, dd, J=10.7, 3.9 Hz, H-6), 3.81–3.92 (~3.3H, m), 3.96 (M) (~0.66H, dd, J=5.7, 3.9 Hz, H-5), 4.02–4.10 (1H, m), 4.11 (M) (~0.66H, broad s, H-4), 4.19 (m) (~0.33H, broad s, H-4), 4.38 (M) (~0.66H, broad s, H-3), 4.42 (m) (~0.33H, broad s, H-3). ^{31}P NMR (101.2 MHz, 300 K, CD_3OD) δ 19.06 (M) (~0.66P, s), 22.10 (m) (~0.33P, s).
5: ^{1}H NMR (500 MHz, 300 K, C_6D_6) δ 1.37 (3H, d, J=7 Hz, CH_3), 2.2 (1H, ddd, J=20.5, 11.5, 9 Hz, H-7), 3.02 (1H, ddd, J=17, 11.5, 7 Hz, H-8), 3.27 (3H, d, 10.5 Hz, -OCH_3), 3.29 (3H, d, 10.5 Hz, -OCH_3), 3.52 (1H, dd, J=9.5, 6 Hz, H-6), 3.58 (1H, t, J=9.5 Hz, H′-6), 3.93 (1H, broad s, H-3), 4.18 (1H, Abq, J=11.5 Hz, -OCH_2Ph), 4.23 (1H, ddd, J=15.5, 9, 3.5 Hz, H-2), 4.26 (1H, Abq, J=12 Hz, -OCH_2Ph), 4.28 (1H, broad s, H-4), 4.30 (1H, Abq, J=9, 6 Hz, H-5), 7.06–7.33 (15H, m, Ph).
12. Selenoxide elimination is known to be *syn* indicating a **7**(*S*) starting selenide. The other isomer should then give rise to *E*-**18**. The observed *E*/*Z* mixture may result from equilibration prior or following selenenic acid elimination. We favour the first possibility, considering the strong acidic character of proton H-7 in the selenoxide derived from **15**.