Tetrahedron Letters 49 (2008) 4167–4169

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of enantiopure ethyl deoxymonate B from allylic sulfinyl dihydropyrans

Roberto Fernández de la Pradilla *, Nadia Lwoff

Instituto de Química Orgánica, CSIC, Juan de la Cierva, 3, 28006 Madrid, Spain

ARTICLE INFO

Article history:
Received 27 March 2008
Accepted 18 April 2008
Available online 23 April 2008

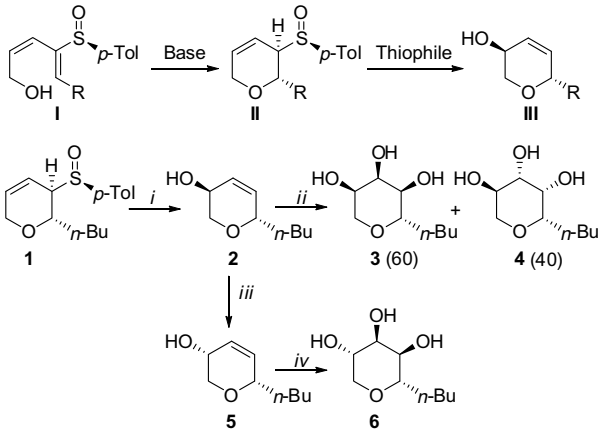
Keywords:
Pseudomonic Acids
Allylic Sulfoxides
Sigmatropic rearrangement
Stereoselective dihydroxylation

ABSTRACT

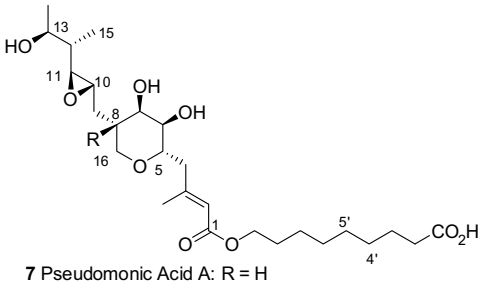
A completely stereoselective dihydroxylation of a dihydropyranol and a cross-metathesis in the presence of a free homoallylic hydroxyl group are the key steps of a synthesis of enantiopure ethyl deoxymonate B from a sulfinyl dienol.

© 2008 Elsevier Ltd. All rights reserved.

The base-promoted cyclization of hydroxy sulfinyl dienes **I** (Scheme 1) affords 2,3-*trans* sulfinyl dihydropyrans with high selectivity.[1] In most cases, these allylic sulfoxides **II** are unusually stable and finding suitable conditions to carry out a synthetically useful sulfoxide sulfenate [2,3]-sigmatropic rearrangement in good yields required considerable experimentation.[2] The use of DABCO in toluene at 70 °C gave consistently high yields of the desired allylic alcohols **III** and this encouraged us to pursue synthetic applications of the methodology.[3,4] Scheme 1 gathers our preliminary results on the osmium-catalyzed dihydroxylation of model *trans* allylic alcohol **2**, readily available from sulfinyl dihydropyran **1**, and its cis diastereomer **5**, prepared from **2** by a Mitsunobu protocol. The dihydroxylation of *trans* allylic alcohol **2** under standard conditions afforded a 60:40 mixture of triols **3** and **4**.[5] In contrast, the dihydroxylation of *cis* allylic alcohol **5** led to triol **6** as a single isomer and in good yield. These results encouraged us to address the application of our methodology to the synthesis of pseudomonic acid B or related compounds (Scheme 2), with a substitution pattern at the tetrahydropyran ring that resembles that of triol **6** (Scheme 1).



Scheme 1. Dihydroxylation of dihydropyranyl allylic alcohols. Reagents and conditions: (i) DABCO, toluene, 70 °C, 91%. (ii) OsO_4, $Me_3NO{\cdot}2H_2O$, rt, 67%. (iii) (a) PPh_3, *p*-nitrobenzoic acid, DIAD, THF, rt; (b) K_2CO_3, MeOH, rt, 71%. (iv) OsO_4, $Me_3NO{\cdot}2H_2O$, rt, 82%.



7 Pseudomonic Acid A: R = H
8 Pseudomonic Acid B: R = OH
9 Pseudomonic Acid C: R = H, C-10/C-11 *E*-alkene
10 Pseudomonic Acid D: R = H, C-4'/C-5' *E*-alkene

Scheme 2. Structure of pseudomonic acids.

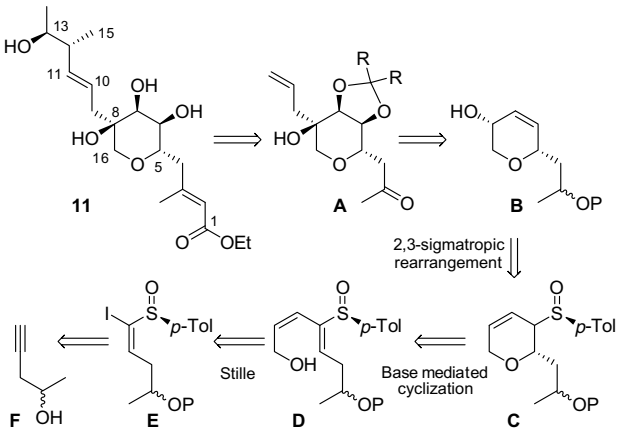
* Corresponding author. Tel.: +34 91 562 29 00; fax: +34 91 564 48 53.
E-mail address: iqofp19@iqog.csic.es (R. Fernández de la Pradilla).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.107

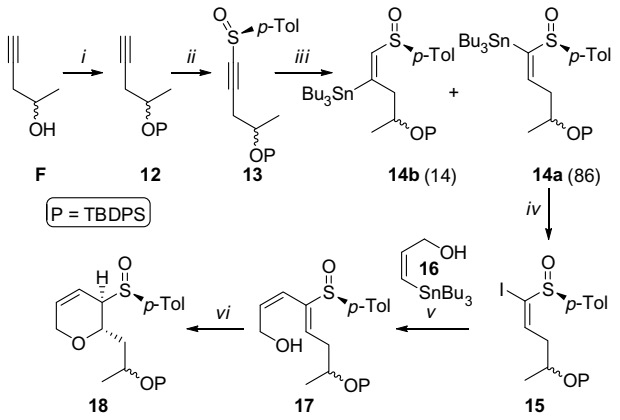
The pseudomonic acids are a family of *C*-glycopyranosides produced by a strain of *Pseudomonas fluorescens*, that present a potent antibiotic activity against gram-positive aerobic bacteria.[6] Pseudomonic acid A **7** is clinically used as a topical antibacterial (Bactroban). This potent activity and their challenging structure have attracted the interest of many groups and this has led to many synthetic approaches over the last two decades.[7] All four pseudomonic acids are structurally related presenting an α-cis-disubstituted tetrahydropyran ring at C-5 and C-8 positions, as well as β-*cis* hydroxyl groups at C-6 and C-7. Pseudomonic acid B presents an additional oxygenated center at C-8 (Scheme 2), and in pseudomonic acid C the C-10/C-11 oxirane is replaced by an *E* alkene. Pseudomonic acid D possesses the same general structure as pseudomonic acid A, except for C-4′/C-5′ *E* double bond. The creation of the key tetrahydropyran core has been pursued by different strategies, such as the use of carbohydrates, Diels–Alder processes or from acyclic precursors. The new stereocenters have been established by a variety of approaches such as Claisen rearrangements, Pd-catalyzed alkylations, or radical processes. The α-cis side chains at C-5 and C-8 have been homologated using several methodologies, including Wittig and Julia processes and cross-metathesis reactions.

There are comparatively few synthetic approaches that address incorporation of the C-8 hydroxyl group for the preparation of pseudomonic acid B and related compounds.[8] Our retrosynthetic analysis for ethyl deoxymonate B, **11**, is outlined in Scheme 3 and entails a key cross-metathesis step to homologate the side chain at C-8 of late intermediate **A** and a Horner-Wadsworth-Emmons reaction to build the C-5 side chain. This cross-metathesis in the presence of a free hydroxyl group at C-8, inspired by the work of Markó,[7g] was considered a challenging but interesting solution to install the side chain. The precursor of intermediate **A** would be allylic alcohol **B**, resulting from the [2,3]-sigmatropic rearrangement of allylic sulfoxide **C**. Sulfinyl dihydropyran **C** would result from the base-mediated cyclization of dienyl sulfoxide **D**, that could be prepared from 4-pentyn-2-ol **F** via iodo vinyl sulfoxide **E** by a Stille coupling process with the required hydroxy vinyl stannane.

Our synthetic efforts toward ethyl deoxymonate B **11**, started from commercially available 4-pentyn-2-ol **F** (Scheme 4). Protection of (rac)-4-pentyn-2-ol with TBDPSCl, and reaction of the protected alkyne **12** with EtMgBr and (–)-menthyl *p*-toluenesulfinate led to alkynyl sulfoxide **13** that afforded an 86:14 mixture of regioisomers **14a** and **14b** by Pd-catalyzed hydrostannylation. Tin–iodine exchange on **14a** led to vinyl iodide **15** that was submitted to a Stille coupling with hydroxy vinyl stannane **16** to give sulfinyl diene **17** in excellent yield. Base-promoted cyclization with



Scheme 3. Retrosynthetic analysis for ethyl deoxymonate B, **11**.

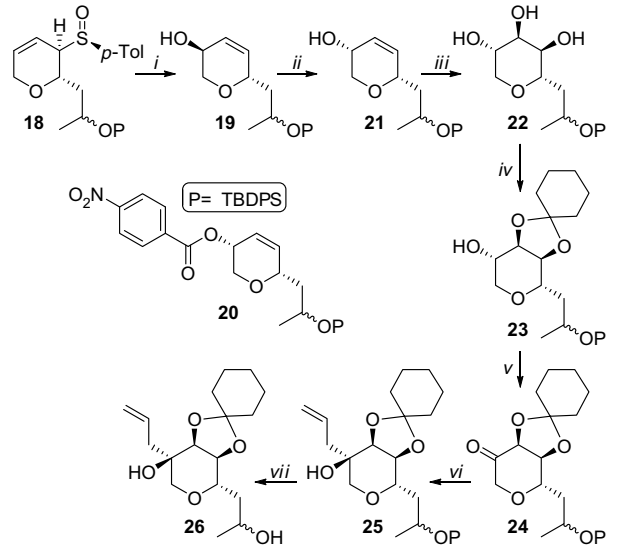


Scheme 4. Synthesis of sulfinyl dihydropyran **18**. Reagents and conditions: (i) TBDPSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 77%. (ii) (a) EtMgBr, Et_2O; (b) (–)-menthyl *p*-toluenesulfinate, toluene, −20 °C, 99%. (iii) Bu_3SnH, $Pd(PPh_3)_4$, toluene −78 °C to rt, 100%. (iv) I_2, CH_2Cl_2, rt, 82%. (v) **16**, Ph_3As, BHT, $Pd_2(dba)_3{\cdot}CHCl_3$, THF, rt, 99%. (vi) LDA, THF, −78 °C to rt, 100%.

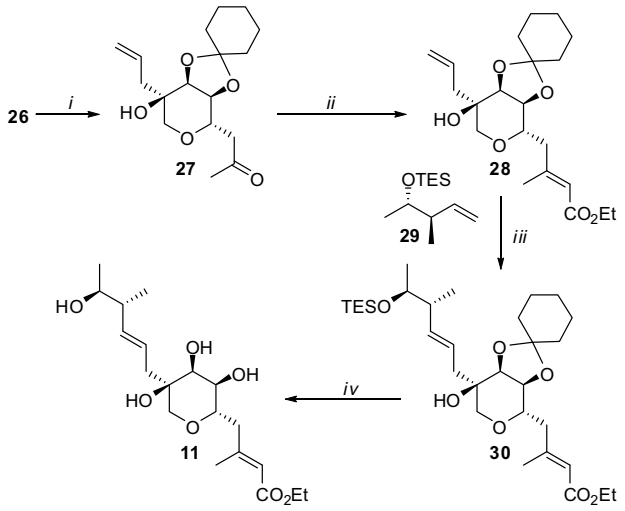
LDA afforded 2,3-*trans* sulfinyl dihydropyran **18** as a single isomer in excellent yield. Thus, the pyran core of the target was built with the appropriate substitution and absolute configuration at C-5.[9]

2,3-Sigmatropic rearrangement of allylic sulfoxide **18** afforded *trans* allylic alcohol **19** as a single isomer (Scheme 5). Our preliminary studies on the dihydroxylation of model substrates indicated that the highest selectivity was obtained for *cis*-disubstituted dihydropyrans. Thus, the allylic alcohol was inverted by a Mitsunobu protocol, via *p*-nitrobenzoate **20**, to produce *cis* alcohol **21**. As expected dihydroxylation with osmium tetroxide afforded triol **22** as the sole product, and the *cis* diol was protected as a cyclohexylidene ketal obtaining **23**.

Alcohol **23** was oxidized to ketone **24** with PCC, and addition of allylmagnesium bromide to the ketone afforded tertiary alcohol **25** exclusively (Scheme 5).[8b] Deprotection of the secondary alcohol on the side chain at C-5 resulted quite slow and led to diol **26** which was oxidized, to produce ketone **27** as a single product that



Scheme 5. Reagents and conditions: (i) DABCO, toluene, 70 °C, 96%. (ii) (a) PPh_3, *p*-nitrobenzoic acid, DIAD, THF, rt, 84%; (b) K_2CO_3, MeOH, rt, 94%. (iii) OsO_4, $Me_3NO{\cdot}2H_2O$, acetone:H_2O (9:1), rt, 96%. (iv) Cyclohexanone, *p*-TsOH, toluene, rt, 86%. (v) PCC, 4 Å MS, CH_2Cl_2, rt, 72%. (vi) allylMgBr, THF, −30 °C to rt, 70%. (vii) TBAF, THF-DMF (8:2), 0 °C to rt, 72%, 6% recovered starting material.



Scheme 6. Synthesis of ethyl deoxymonate B **11**. Reagents and conditions: (i) PCC, 4 Å MS, CH_2Cl_2, rt, 86%. (ii) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, −70 °C to rt, 34%, 60% recovered starting material. (iii) **30**, Grubbs second generation catalyst, toluene, 55 °C, 66%. (iv) DOWEX, MeOH, rt, 80%.

appeared to be stable to ketal migration (Scheme 6).[10] The Wittig reaction of **27** with the sodium anion of triethyl phosphonoacetate afforded **28** as an 80:20 mixture of *E*/*Z* isomers[11] that was used as a mixture in the next step. These results could probably be improved with a thorough study of the conditions for this step, to obtain higher yield and selectivity. Homologation of the C-8 side chain was carried out using the same conditions described by Markó et al. for a related system lacking the extra hydroxyl group at the homoallylic position.[7g] To our delight, the cross-metathesis of **28** and fragment **29**, prepared in four steps from ethyl (*S*)-3-hydroxybutyrate,[12] afforded **30** as an *E*/*Z* mixture, with the *E* isomer as the major product, with just *E* geometry at the C-10/C-11 alkene. Subsequent purifications afforded *E* **30** contaminated with traces of *Z* isomer at C-2. The spectral data for **30** (^{1}H NMR) were almost identical to that of a similar product described in the literature.[8b]

The synthetic sequence was completed by cleavage of the silyl ether and cyclohexylidene ketal upon treatment of **30** with DOWEX affording ethyl deoxymonate B **11** (2.2%) in 17 linear steps (21 steps total) from commercially available 4-pentyn-2-ol (Scheme 6). The previous synthesis obtained the related methyl deoxypseudomonate B in 21 linear steps (29 steps total) from L-lyxose.[8b]

In summary, readily available enantiopure allylic sulfinyl dihydropyrans have been transformed smoothly into allylic dihydropyranols that undergo a highly selective osmium-catalyzed dihydroxylation in some cases. This methodology has been applied to a synthesis of ethyl deoxymonate B that features a homologation of the C-8 side chain by a cross-metathesis of a homoallylic free alcohol fragment.

Acknowledgements

This research was supported by DGI MEC (CTQ2006-04522/BQU) and CM (S-SAL-0249-2006). We thank JANSSEN-CILAG for generous additional support and MEC for a doctoral fellowship to NL. We are grateful to Dr. J. L. Chiara (IQOG, CSIC) for fruitful discussions.

References and notes

1. Fernández de la Pradilla, R.; Tortosa, M. *Org. Lett.* **2004**, *6*, 2157–2160.
2. (a) Rayner, D. R.; Miller, E. G.; Bickart, P.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc.* **1966**, *88*, 3138–3139; (b) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869–4876; (c) Braverman, S.; Stabinsky, Y. *J. Chem. Soc., Chem. Commun.* **1967**, 270; (d) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956–4957.
3. A full account of this study will be published elsewhere.
4. For an application to the formal synthesis of *ent*-dysiherbaine, see: Fernández de la Pradilla, R.; Lwoff, N.; Viso, A. *Tetrahedron Lett.* **2007**, *48*, 8141–8144.
5. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.
6. (a) Badder, C.; Garre, C. *Corresp.-Bl. Sweiz. Aerzte* **1887**, *17*, 385; (b) Fuller, A. T.; Mellows, G.; Woolford, M.; Banks, G. T.; Barrow, K. D.; Chain, E. B. *Nature* **1971**, *234*, 416–417.
7. For a review see: (a) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843–1857. and references therein; For syntheses and synthetic approaches see: (b) Balog, A.; Yu, M. S.; Curran, D. P. *Synth. Commun.* **1996**, *26*, 935–944; (c) Khan, N.; Xiao, H. Y.; Zhang, B.; Cheng, X. H.; Mootoo, D. R. *Tetrahedron* **1999**, *55*, 8303–8312; (d) McKay, C.; Simpson, T. J.; Willis, C. L.; Forrest, A. K.; O'Hanlon, P. J. *Chem. Commun.* **2000**, 1109–1110; (e) Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4529–4535; (f) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 3359–3361; (g) van Innis, L.; Plancher, J. M.; Markó, I. E. *Org. Lett.* **2006**, *8*, 6111–6114.
8. (a) Schönenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333–2337; (b) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1984**, *25*, 2085–2088; (c) Honda, T.; Kimura, N. *Org. Lett.* **2002**, *4*, 4567–4570.
9. Since our synthetic plan included the oxidation of the secondary alcohol of the C-5 side chain, the isomers were not separated and all products were characterized as equimolar mixtures of diastereoisomers before oxidation.
10. We had observed partial migration of the ketal protecting group upon standing when an isopropylidene derivative was used. A full account of these results will be described in due time.
11. Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577–6580.
12. The scale in the preparation of fragment **29** proved to be critical. No methylation of ethyl (*S*)-3-hydroxybutyrate was observed at small scale or in the absence of DMPU.