Pergamon

Tetrahedron Letters 40 (1999) 5499–5502

TETRAHEDRON LETTERS

En route toward squalestatins and analogues from furfuryl alcohol and maleic anhydride

Nathalie Jotterand and Pierre Vogel *

Section de Chimie de l'Université de Lausanne, BCH, CH 1015 Lausanne-Dorigny, Switzerland

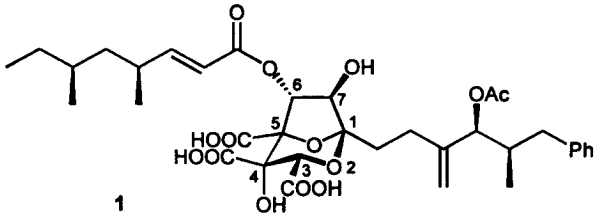
Received 26 April 1999; accepted 28 May 1999

Abstract

The Diels–Alder adduct of furfuryl alcohol and maleic anhydride was converted into a 3,4,5-trihydroxy-9-oxo-8-oxabicyclo[4.3.0]non-1(6)-ene-2-carboxylic derivative, then into polyhydroxylated systems containing three contiguous, oxidized, one-carbon side-chains that are potential intermediates in the synthesis of 6-*epi*-squalestatins and analogues. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: dihydroxylation; 7-oxabicyclo[2.2.1]heptenes; oxidations; zaragozic acids.

In 1992, the Merck group, the Glaxo group and authors from the University of Tokyo Noko reported independently the discovery of new, potent inhibitors of squalene synthase and farnesyl-protein transferase named zaragozic acids or squalestatins (e.g. zaragozic acid A, **1**). These compounds have in common a polyhydroxylated 2,8-dioxabicyclo[3.2.1]octane core bearing three contiguous carboxylic groups.[1]



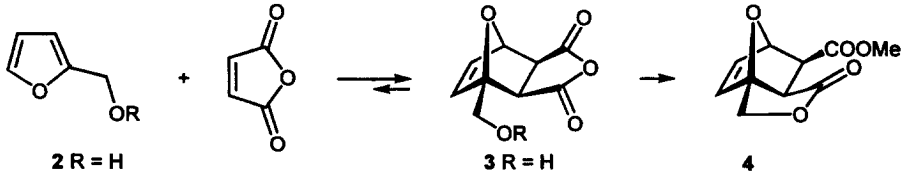
1

Already seven total syntheses of squalestatins have appeared[2] as well as several reports describing efforts toward the preparation of these compounds and analogues.[3] Recently, Nagaoka and co-workers[4] have apprcached the synthesis of the core of squalestatins starting from the Diels–Alder adduct of furan-2,5-dimethanol and dimethyl acetylenedicarboxylate. Their report urges us to disclose our own efforts toward the total synthesis of squalestatins based on the Diels–Alder adduct (±)-**3** of furfuryl alcohol (**2**) and maleic anhydride. This choice of starting material was motivated by the fact that adduct (+)-**6** of furfuryl (1*S*)-camphanate ((+)-**5**) and maleic anhydride is highly diastereoselective under conditions of thermodynamic control, allowing one to generate in one step the 7-oxabicyclo[2.2.1]heptene derivative

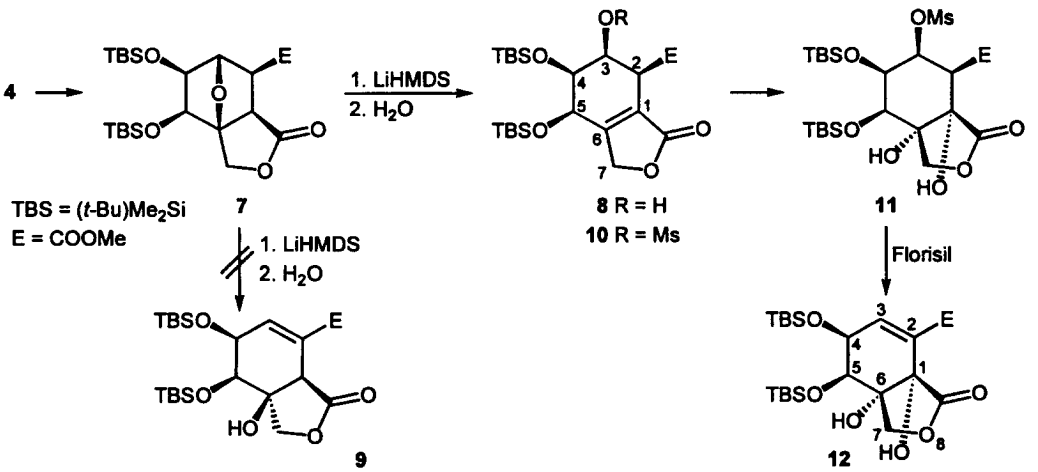
* Corresponding author. Fax: +41 21 692 39 75; e-mail: pierre.vogel@ico.unil.ch

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01068-0

(−)-**4** enantiomerically pure,[5] a system that possesses all the carbon atoms of the bicyclic core of the squalestatins. We report here reactions that convert (±)-**4** into potential synthetic precursors of 6-*epi*-squalestatins and analogues.

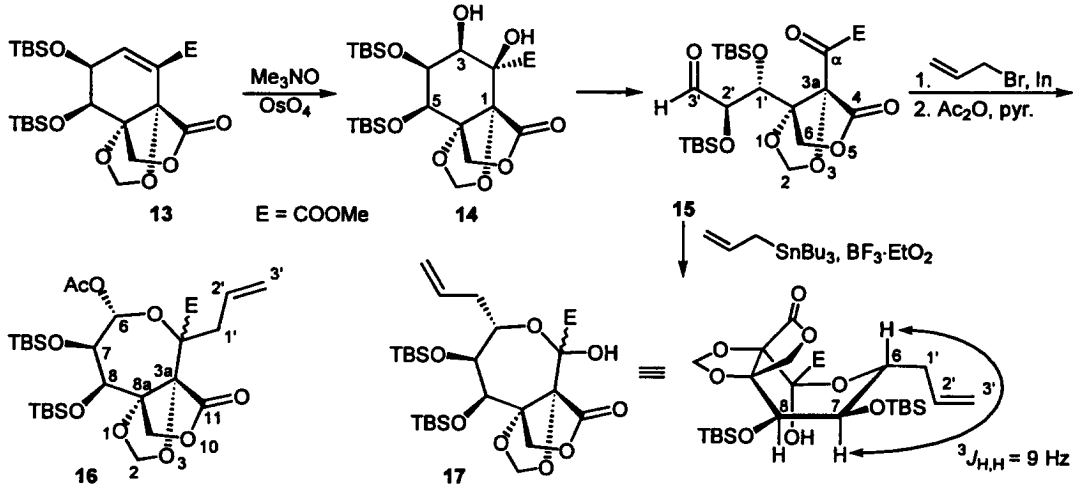


Double hydroxylation of the alkene moiety of (±)-**4** was highly *exo* face selective using H_2O_2/acetone/OsO_4 cat. giving the corresponding diol that was silylated with (*t*-Bu)Me_2SiCl and imidazole into **7** (80%). Regioselective based-induced etheral bridge opening of **7** was possible by adding slowly a 1 M solution of $(Me_3Si)_2NLi$ in THF to a THF solution of **7** cooled to −78°C. This provided **8** in 99% yield after purification. Epimerization of the ester **8** was observed when the addition of the $(Me_3Si)_2NLi$ addition was too fast. The high regioselectivity of the isomerization **7**→**8** is remarkable. It is probably the manifestation of the greater ring strain relief for reaction **7**→**8** than for the alternative isomerization **7**→**9**. Double hydroxylation of the tetrasubstituted olefinic moiety of **8** was possible with Me_3NO and OsO_4 (cat.),[6] but the yield of the corresponding triol never surpassed 36%. Esterification of alcohol **8** with CH_3SO_2Cl/pyridine in CH_2Cl_2 (20°C, 15 h) afforded the mesylate **10** (94% yield). This was dihydroxylated with $NaIO_4$ and $RuCl_3$ hydrate (cat.)[6] in a mixture of MeCN/EtOAc/H_2O (20°C, 2 h) into diol **11** that was not isolated as its purification by flash chromatography on Florisil liberated the product of mesylic acid elimination **12** isolated in 60% yield.[7] The *trans* relative configuration of the diol and bis(silyloxy) substituent pairs in **11** and **12** was established as shown below. Molecular models suggest that the stereoselectivity observed for reaction **10** → **11** is due to a steric factor, the face of the alkene moiety *anti* to the silyloxy and methoxycarbonyl groups being less sterically hindered than the *syn* face.

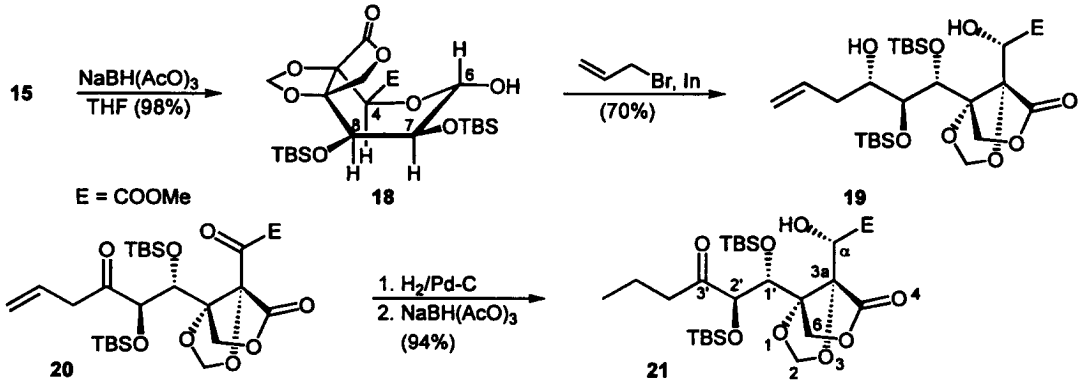


Treatment of diol **12** with $(MeO)_2CH_2$ and P_2O_5 gave the methylidene acetal **13** (88% yield). Attempts to cleave the trisubstituted alkene unit **13** with ozone all failed. We thus exposed **13** to Me_3NO and OsO_4 (cat.) in 8:1 acetone:water; this led to diol **14** (95% yield) with high diastereoselectivity, the latter being not yet established unambiguously. Oxidative cleavage of diol **14** with $Pb(OAc)_4$[8] in CH_2Cl_2 (25°C) provided oxoaldehyde **15** (95% yield).[9] Reaction of **15** with allyl bromide and indium[10] gave a mixture of aldoses that were acetylated (Ac_2O/pyridine, 25°C) into acylal **16** (45% yield).[11] Its configuration at

C-2 has not been established, that at C-7 was given by ^3J(H-6, H-7)=8.3 Hz in its ^{1}H NMR spectrum. Allylation of **15** with allyltributyltin in the presence of $BF_3 \cdot Et_2O$[12] furnished ulose **17** (one major anomer, 42% yield),[13] the relative configuration of which at C-6 was given by ^3J(H-6, H-7)=9 Hz in its ^{1}H NMR spectrum. The 2D NOESY ^{1}H NMR spectrum of **17** showed cross-peaks that confirmed the structures of **17** and of its precursors (*cis–syn* dihydroxylation **10** → **11**).



Chemoselective reduction of oxoaldehyde **15** was possible with $NaBH(AcO)_3$ in THF[14] (20°C, 3 h) giving hemiacetal **18** (one major anomer, 90% yield)[15] resulting from the reduction of the keto moiety activated by the α-carboxylic function. The relative configuration of C-4 was confirmed by the observation of NOE's between signals at δ_H 4.79 (H-4), 4.42 (H-7) and 3.89 ppm (H-8) in the 2D NOESY ^{1}H NMR spectrum of **18**. Except for the γ-lactone part, compound **18** has the same 'oxidation state' (type of oxy-substitution) as the core of 6-*epi*-squalestatins.



Allylation of **18** with allyl bromide and indium provided **19** (70% yield) which was oxidized (Dess–Martin periodinane[16]) into diketone **20**. Treatment of **20** with $NaBH(AcO)_3$ failed to give the corresponding hydroxyketone, probably because of a competitive intramolecular aldol condensation. Catalytic hydrogenation of **20** (H_2/Pd-C), followed by treatment with $NaBH(AcO)_3$ in THF generated **21** (94% yield, two steps).[17,18]

Our report discloses procedures for the selective oxy-substitution and ethereal ring opening of 7-oxabicyclo[2.2.1]heptene (±)-**4**, generating a variety of polyhydroxylated cyclohexenes and cyclohexanes bearing three contiguous, oxidized, one-carbon side-chains. Some of these systems are potential intermediates for the synthesis of 7-*epi*-squalestalins and analogues. The latter can be prepared optically pure in both enantiomeric forms as (+)-**4** and (−)-**4** are both readily available.[5]

Acknowledgements

We thank the Swiss National Science Foundation and the Stipendienfonds der Basler Chemischen Industrie for financial support.

References

1. For a review, see: Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622.
2. (a) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2190; Nicolaou, K. C.; Yue, E. W.; Naniwa, Y.; De Riccardis, F.; Nadin, A.; Leresche, J. E.; La Greca, S.; Yang, Z. *Ibid.* **1994**, *33*, 2184; (b) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115; Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *Ibid.* **1996**, *61*, 9126; (c) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825; **1995**, *117*, 8106; (d) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 12111; (e) Sato, H.; Nakamura, S.-I.; Watanabe, N.; Hashimoto, S. I. *Synlett* **1997**, 451; (f) Armstrong, A.; Jones, L. H.; Barsanti, P. A. *Tetrahedron Lett.* **1998**, *39*, 3337; (g) Martin, S. F.; Naito, S. *J. Org. Chem.* **1998**, *63*, 7562.
3. See Ref. 1 and: Ito, H.; Matsumoto, M.; Yoshizawa, T.; Takao, K.-I.; Kobayashi, S. *Tetrahedron Lett.* **1997**, *38*, 9009; Xu, Y.; Johnson, C. R. *Ibid.* **1997**, *38*, 1117; Paterson, I.; Fessner, K.; Finlay, M. R. *Ibid.* **1997**, *38*, 4301; Reid, A. M.; Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2795; Mann, R. K.; Parsons, J. G.; Rizzacasa, M. A. *Ibid.* **1998**, 1283; Brogan, J. B.; Zercher, K. C. *Tetrahedron Lett.* **1998**, *39*, 1691; Kataoka, O.; Kitagaki, S.; Watanabe, N.; Kobayashi, J.-I.; Nakamura, S.-I.; Shiro, M.; Hashimoto, S. I. *Ibid.* **1998**, *39*, 2371; Freeman-Cook, K. D.; Halcomb, R. L. *Ibid.* **1998**, *39*, 8567; Tsubuki, M.; Okita, H.; Honda, T. *Synlett* **1998**, 1417 and references cited therein.
4. Koshimizu, H.; Baba, T.; Yoshimitsu, T.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 2777.
5. Theurillat-Moritz, V.; Vogel, P. *Tetrahedron: Asymmetry* **1996**, *7*, 3163; the same method starting from furfuryl (1*R*)-camphanate allows one to obtain enantiomer (+)-**4** with the same ease.
6. Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Shung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50.
7. Data for (±)-**12**: m.p. 117–118.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): 6.22 (br. *s*, OH), 6.76 (*dd*, ^3J=^4J=1.7, H-3), 4.89 (*dd*, ^3J=2.1, 1.7, H-4), 4.32, 4.21 (2*d*, ^2J=9.2, $H_2C(7)$), 4.08 (*dd*, ^3J=2.1, ^4J=1.7, H-5), 3.89 (*s*, MeO), 3.50 (*s*, OH), 0.96, 0.83 (2*s*, 2 *t*-Bu), 0.16, 0.15, 0.13, 0.11 (4*s*, 2 Me_2Si).
8. Pianetti, P.; Rollin, P. *Tetrahedron Lett.* **1986**, *27*, 5853; Achmatowicz, B.; Micha, J. *Ibid.* **1987**, *28*, 2999.
9. Data for (±)-**15**: m.p. 94–95.5°C; IR (film): 2930, 2885, 2860, 2360, 1790, 1730, 1360, 1320; ^{1}H NMR (400 MHz, $CDCl_3$): 9.62 (*s*), 5.47, 5.18 (2*s*), 4.79, 4.52 (2*d*, ^2J=9.8, H_2-6), 4.36 (*d*, ^3J=1.7, H-2′), 4.09 (*d*, ^3J=1.7, H-1′), 3.95 (*s*, MeO), 0.96, 0.84 (2*s*), 0.13, 0.11, 0.09, 0.01 (4*s*).
10. Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.
11. Data for (±)-**16**: oil; IR (film): 2960, 2930, 2860, 1790, 1765, 1735; ^{1}H NMR (400 MHz, $CDCl_3$): 6.61 (*d*, ^3J=8.3, H-6), 5.85 (*ddt*, ^3J=9.3, 9.0, 4.5, H-2′), 5.32, 4.90 (2*s*, H_2-2), 5.04 (*ddd*, ^2J=2.0, ^3J=9.0, ^4J=2.0, H-3′), 5.00 (br. *d*, ^2J=2.0, H-3′), 4.78, 4.29 (2*d*, ^2J=9.9, H_2-9), 4.05 (br. *s*, H-8), 3.94 (*dd*, ^3J=8.3, 0.6, H-7), 3.79 (*s*, MeO), 3.25 (*dd*, ^2J=15.0, ^3J=9.3, H-1′), 3.01 (*ddd*, ^2J=15.0, ^3J=4.5, 2.0, H-1′), 2.16, 0.94, 0.91, 0.17, 0.15 (5*s*).
12. Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.
13. Data for (±)-**17**: oil; ^{1}H NMR (400 MHz, $CDCl_3$): 5.78 (*ddt*, ^3J=17.5, 10.0, 7.0, H-2′), 5.42, 4.86 (2*s*, H_2-2), 5.04 (*ddd*, ^2J=3.5, ^3J=17.0, 1.3, H-3′), 5.00 (*ddd*, ^2J=3.5, ^3J=10.0, 1.3, H-3′), 4.91, 4.31 (2*d*, ^2J=10.2, H_2-9), 4.50 (*ddd*, ^3J=11.0, 9.0, 2.4, H-6), 4.08 (*s*, H-8), 3.97 (*s*, MeO), 3.94 (*d*, ^3J=9.0, H-7), 2.50 (*dddt*, ^2J=15.0, ^3J=7.0, 2.4, 1.3, H-1′), 2.22 (*dddt*, ^2J=15.0, ^3J=11.0, 7.0, 1.3, H-1′), 0.94, 0.21, 0.15, 0.13 (4*s*).
14. Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535; Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
15. Data for (±)-**18**: ^{1}H NMR (400 MHz, $CDCl_3$): 5.37, 4.99 (2*s*, H_2-2), 5.20, 3.92 (2*d*, ^2J=10.2, H_2-9), 5.14 (br. *s*, H-6), 4.79 (*s*, H-4), 4.42 (*s*, H-7), 3.89 (*s*, H-8), 3.85 (*s*, MeO), 3.83 (br. *s*, OH), 0.92, 0.91, 0.15, 0.14 (4*s*).
16. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; Ireland, R. E.; Liu, L. *Ibid.* **1993**, *58*, 2899.
17. Data for (±)-**21**: oil; ^{1}H NMR (400 MHz, $CDCl_3$): 5.38, 5.11 (2*d*, ^2J=1.8, H_2-2), 4.74 (*d*, ^3J=2.2, H-2′), 4.68 (*d*, ^3J=4.0, Hα), 4.60, 4.07 (2*d*, ^2J=9.7, H_2-6), 3.95 (*s*, MeO), 3.93 (*d*, ^3J=2.2, H-1′), 3.56 (*d*, ^3J=4.0, OH), 2.67, 2.57 (2*ddd*, ^2J=18.7, ^3J=7.8, 6.7, H_2-4′), 1.60 (*m*, H_2-5′), 0.96, 0.93 (2*s*), 0.92 (*m*, H_3-6′), 0.35, 0.23, 0.13, 0.12 (4*s*).
18. All the new compounds gave satisfactory elemental analyses.