Pergamon

Tetrahedron Letters, Vol. 35, No. 32, pp. 5841-5844, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01208-3

A Short Route to Avenaciolide & Isoavenaciolide via Radical Cyclization

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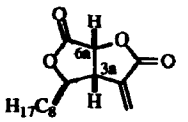
Key Words: avenaciolide; isoavenaciolide; radical cyclization; Pummerer rearrangement

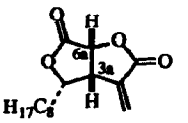
Abstract: *The bicyclic ether/lactone **5** was prepared from **7** in 6 steps including radical cyclization and a Pummerer rearrangement. After **5** was converted to **12** and **13** under Keck's conditions, divergent formal total syntheses of avenaciolide and isoavenaciolide were accomplished in four additional steps.*

Avenaciolide (**1**)[1] and isoavenaciolide (**2**)[2] are secondary metabolites isolated from the fermentation broth of *Aspergillus* and *Penicillium* species, which exhibit diverse and potent biological activity. In particular, avenaciolide inhibits fungal spore germination, displays antibacterial action,[1a] and inhibits glutamate transport in rat liver mitochondria.[3]

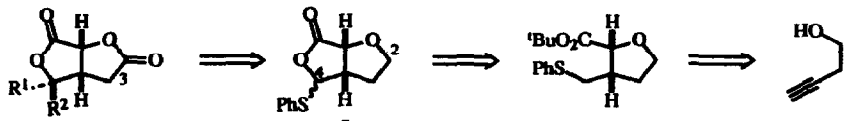
Scheme I



Avenaciolide (1)



Isoavenaciolide (2)



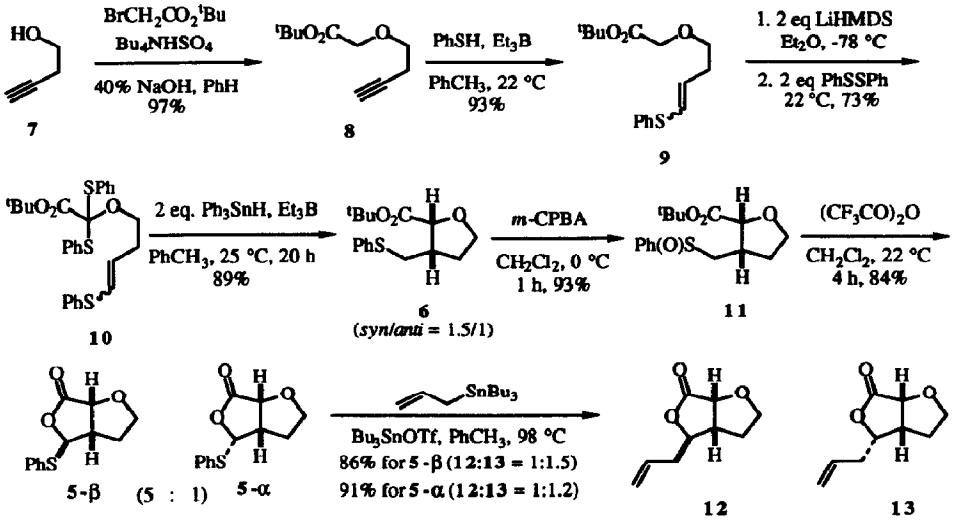
3; R^1 = H, R^2 = *n*-C_8H_{17}
4; R^1 = *n*-C_8H_{17}, R^2 = H

5 **6** **7**

In the course of the study on tetrahydrofuran synthesis (see preceding paper), the *syn* 2,3-disubstituted tetrahydrofuran **6** was obtained and converted to the bicyclo[3.3.0]ether/lactone **5** for the elucidation of its stereochemistry (**Scheme I**).[4] Not only do these compounds include the C(3a) and C(6a) stereogenic centers of avenaciolide and isoavenaciolide, but **5** has the necessary bicyclic ring skeleton. These structural features prompted a synthesis of the two natural metabolites from **5** as a common intermediate.[5]

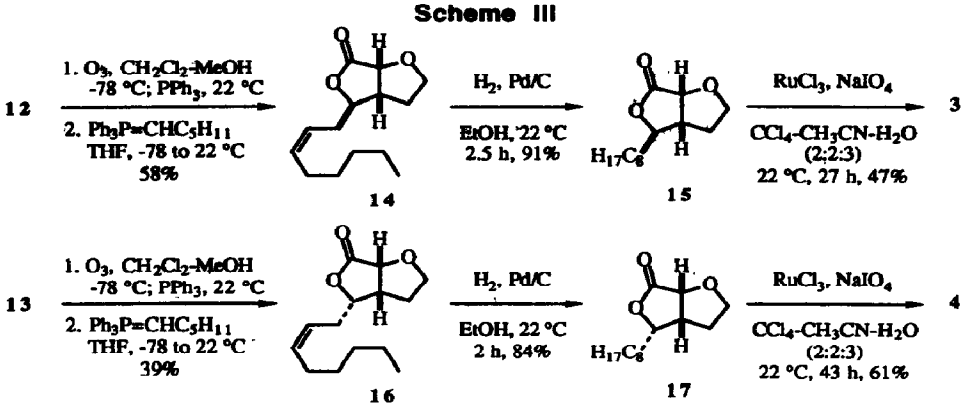
As shown retrosynthetically in **Scheme I**, 3-normethylene analogs **3** and **4** have repeatedly served as intermediates in the total syntheses of avenaciolide and isoavenaciolide, respectively, and these were also selected as the target molecules of our synthesis. The bislactones **3** and **4** could be made divergently from the bicyclic intermediate **5** by the introduction of the octyl side chain at the C(4) center and oxidation of the C(2) methylene. As seen in the preceeding report, the preparation of **5** requires 4-6 steps from the commercially available alcohol **7**, depending on a choice among three different reaction sequences involving radical cyclization.

Scheme II



The preparation of the divergent intermediates **12** and **13** for the synthesis of avenaciolide and isoavenaciolide is described in **Scheme II**. The phase transfer *O*-alkylation of 3-butyn-1-ol produced the alkyne **8** in excellent yield, which was subsequently converted to vinyl sulfide **9** under mild radical conditions.[6] After bis(phenylsulfenylation), the resulting radical cyclization precursor **10** was treated with two equivalents of triphenylstannane at 25 °C to provide the *syn* diastereomer **6** as the slightly favored product. The minor *anti* isomer could be recycled to the desired isomer by the kinetic protonation of the derived ester enolate.[7] Treatment of sulfide **6** with slightly less than one equivalent of *m*-chloroperoxybenzoic acid at 0 °C afforded sulfoxide **11** in 93% yield as an inconsequential mixture at sulfur, with less than 5% recovery of starting material. Subsequent implementation of the Pummerer rearrangement/intramolecular trapping[8] made possible the elucidation of the stereochemistry of the tetrahydrofurans resulted from the radical cyclization.[4] When sulfoxide **11** was treated with excess trifluoroacetic anhydride in dry CH_2Cl_2, the bicyclic products **5**-β and **5**-α[9] were generated in a ratio of 5:1. These separable diastereomers were converted to olefins **12** and **13** under Keck's *C*-glycosylation conditions[10] using allyltributylstannane and a catalytic amount of tributyltin trifluoromethanesulfonate,[11] with similar diastereoselectivities.

Scheme III



The formal total syntheses of avenaciolide and isoavenaciolide were realized by preparing the known intermediates **3**[12] and **4**[13] as delineated in **Scheme III**. Utilizing an ozonolysis-Wittig homologation sequence, chain elongation was accomplished on **12** and **13** to furnish (*Z*) olefins **14** and **16** via the extremely unstable aldehydes. Catalytic hydrogenation proceeded smoothly, giving rise to **15** and **17**, which were subjected to oxidation[14] to provide the 3-normethyleneavenaciolide **3** and the 3-normethyleneisoavenaciolide **4**, respectively. The bislactones **3**[12] and **4**[13] were spectroscopically identical to those reported previously in the literature.

In conclusion, the current sequence provides a short (overall 9 or 11 steps), divergent route to racemic avenaciolide and isoavenaciolide, wherein a new synthesis of the bicyclic bislactone skeleton, featuring radical cyclization and a Pummerer rearrangement, is demonstrated.

Acknowledgments: Financial support for this work in the form of a Bristol-Myers Squibb Graduate Fellowship (K.W.J.) and a Pfizer Undergraduate Fellowship (R.E.P.) is gratefully acknowledged, as is support from the National Institutes of Health (GM 31998).

REFERENCES AND NOTES

1. For the isolation and structure of avenaciolide, see: (a) Brookes, D.; Tidd, B. K.; Turner, W. B. *J. Chem. Soc.* **1963**, 5385. (b) Ellis, J. J.; Stodola, F. H.; Vesonder, R. F.; Glass, C. A. *Nature (London)* **1964**, *203*, 1382. (c) Brookes, D.; Sternhell, S.; Tidd, B. K.; Turner, W. B. *Aust. J. Chem.* **1965**, *18*, 373. (d) Hughes, D. L. *Acta Crystallogr.* **1978**, *B34*, 3674. For the syntheses of avenaciolide, see: (e) Parker, W. L.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489. (f) Parker, W. L.; Johnson, F. *J. Am. Chem. Soc.* **1969**, *91*, 7208. (g) Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4781. (h) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 3657. (i) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544. (j) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 7923. (k) Kido, F.; Tooyama, Y.; Noda, Y.; Yoshikoshi, A. *Chem. Lett.* **1983**, 881. (l) Takei, H.; Fukuda, Y.; Taguchi, T.; Kawara, T.; Mizutani, H.; Mukuta, T. *Chem. Lett.* **1980**, 1311. (m) Sakai, T.; Horikawa, H.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 2039. (n) Murai, A.; Takahashi, K.; Taketsuru, H.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1981**, 221. (o) Schreiber, S. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200. (p) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1985**, *50*, 1128. (q) Kotsuki, H.; Ohnishi, H.; Akitomo, Y.; Ochi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3881.

(r) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 6237. (s) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron* **1988**, *44*, 4061. (t) Tsuboi, S.; Sakamoto, J.; Sakai, T.; Utaka, M. *Chem. Lett.* **1989**, 1427. (u) Sharma, G. V. M.; Vepachedu, S. R. *Tetrahedron Lett.* **1990**, *31*, 4931. (v) Mikami, K.; Shimizu, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 2952. (w) Snider, B. B.; McCarthy, B. A. *Tetrahedron* **1993**, *49*, 9447. (x) Udding, J. H.; Tuijp, K. J. M.; van Zanden, M. N. A.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 1993.

2. For the isolation and structure of isoavenaciolide, see: (a) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1971**, 2431. For the syntheses of isoavenaciolide, see: (b) Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1977**, 2865. (c) Reference 1g. (d) Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1975**, 4551. (e) Yamada, K.; Kato, M.; Iyoda, M.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 499. (f) References 1r and 1s. (g) McDonald, C. E.; Dugger, R. W. *Tetrahedron Lett.* **1988**, *29*, 2413. (h) Wee, A. G. H. *Tetrahedron* **1990**, *46*, 5065. For correction, see: *Tetrahedron* **1993**, *49*, 1335. (i) Chida, N.; Tobe, T.; Suwama, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1990**, 994. (j) Chida, N.; Tobe, T.; Suwama, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2667. (k) Reference 1x.
3. (a) Meyer, J.; Vignais, P. M. *Biochem. Biophys. Acta* **1973**, *325*, 375. (b) McGivan, J. D.; Chappell, J. B. *Biochem. J.* **1970**, *116*, 37P.
4. The *syn* diastereomer **6** was converted to the bicyclic product **5** while the *anti* isomer did not give the corresponding *trans* fused bicyclic product under the same conditions.
5. For previous syntheses of avenaciolide and isoavenaciolide from these laboratories, see: (a) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345. (b) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228. (c) Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445.
6. For previously used conditions, see: (a) Trofimov, B. A.; Gusarova, N. K.; Atavin, A. S.; Amosova, S. V.; Gusarov, A. V.; Kazantseva, N. I.; Kalabin, G. A. *J. Org. Chem. USSR (Engl. Transl.)* **1973**, *9*, 6. (b) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1985**, *50*, 2569.
7. As the proton source, 2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene, BHT) was used to give a 1:1 diastereomeric mixture.
8. (a) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1969**, *34*, 3618. (b) Russell, G. A.; Mikol, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 5498.
9. The major isomer **5**-β was recrystallized from diethyl ether and its structure was confirmed by single crystal X-ray diffraction analysis.
10. (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. (b) Keck, G. E.; Enholm, E. J.; Kachensky, D. F. *Tetrahedron Lett.* **1984**, *25*, 1867. (c) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 4317.
11. Xian, Y. T.; Four, P.; Guibé, F.; Balavoine, G. *Nouv. J. Chim.* **1984**, *8*, 611.
12. For the *exo*-methylenation and spectral data, see references 1e, 1g, 1o, 1q, 1s and 1x.
13. For the *exo*-methylenation and spectral data, see references 1g, 1s, 1x, 2h and 2j.
14. (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Nuñez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 1928.

(*Received in USA* 17 *May* 1994; *accepted* 16 *June* 1994)