

## A Formal Total Synthesis of (–)-Isoavenaciolide from L-Quebrachitol

Noritaka Chida, Takahiko Tobe, Masami Suwama, Masami Ohtsuka, and Seiichiro Ogawa\*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

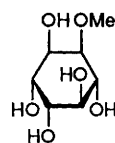
The naturally occurring optically active cyclitol, quebrachitol (**1**), was transformed into the known intermediate (**17**) for preparation of (–)-isoavenaciolide (**2**).

Carbohydrates, especially aldohexoses and pentoses, have frequently been used for syntheses of enantiomerically pure natural products.<sup>1</sup> However, cyclitols have not been used so widely for the synthesis of natural products<sup>2</sup> in spite of their abundance in nature. We now report the synthesis of the structurally interesting bislactone (–)-isoavenaciolide (**2**), the antifungal mould metabolite isolated from *Aspergillus avenaceus*,<sup>3</sup> starting from L-(–)-quebrachitol (**1**). Isoavenaciolide has been synthesized in racemic form,<sup>4</sup> and as its natural enantiomer from D-glucose,<sup>5</sup> D-ribose,<sup>6</sup> and a non-carbohydrate precursor.<sup>7</sup> Although quebrachitol (**1**), a naturally occurring optically active cyclitol, is readily available from the serum of the rubber tree,<sup>8,9</sup> there have been only a few reports on its use in the synthesis of natural products.<sup>9,10</sup>

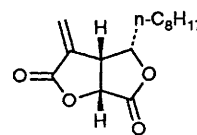
The known diol (**3**),<sup>9</sup> prepared from (**1**) in three steps in 77% overall yield, was treated with toluene-*p*-sulphonyl chloride (1.1 mol equiv.) in pyridine to give a mixture of the two monotosylates (**4**) and (**5**) and the ditosylate (**6**) in 34, 32, and 19% yields, respectively. Base treatment of compound (**4**), followed by reduction of the resulting epoxide with lithium aluminium hydride, gave (**7**) in 72% yield, after acetylation. Debenzylation and subsequent oxidation using

pyridinium chlorochromate (PCC)<sup>11</sup> afforded the ketone (**8**), whose Wittig reaction with Ph<sub>3</sub>P=CHCO<sub>2</sub>Et in toluene gave (**9**) in 84% overall yield from (**7**) as an inseparable mixture (6:1) of *E*- and *Z*-isomers.

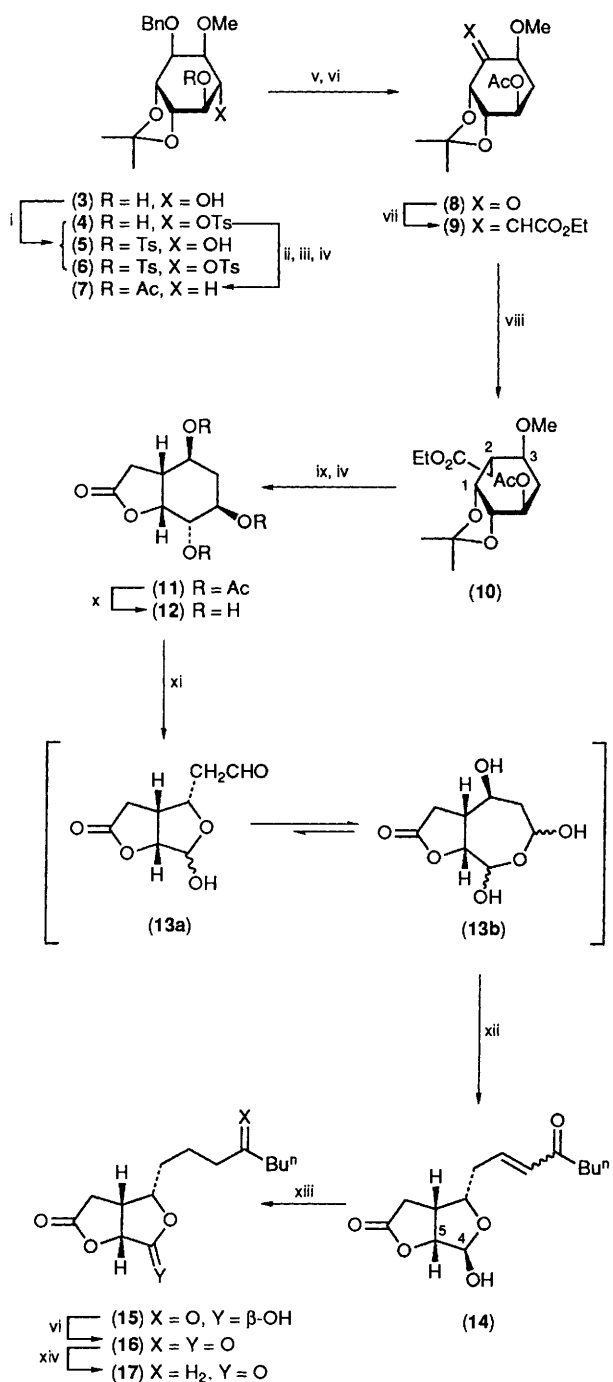
Hydrogenation of the double bond in (**9**) with Raney nickel proceeded stereoselectively, and a 35:1 mixture of compound (**10**) and its 2-epimer was obtained in 96% yield. Treatment of the mixture with boron tribromide in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature caused deprotection of the methyl acetyl and ketal groups, as well as lactonization, to give the γ-lactone (**12**), which was purified as its triacetate (**11**) in 76% yield from (**10**). Acid hydrolysis of (**11**) regenerated (**12**), which was then



(1)



(2)



**Scheme 1.** Bn = PhCH<sub>2</sub>, Ts = *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>. Reagents and conditions: i, TsCl, pyridine, 50 °C; ii, MeONa, MeOH; iii, LiAlH<sub>4</sub>, tetrahydrofuran (THF), room temp.; iv, Ac<sub>2</sub>O, pyridine; v, H<sub>2</sub>, Pd(OH)<sub>2</sub>, EtOH–AcOEt (1:1); vi, pyridinium chlorochromate (PCC), molecular sieves 4A, CH<sub>2</sub>Cl<sub>2</sub>; vii, Ph<sub>3</sub>P=CHCO<sub>2</sub>Et, toluene, room temp., viii, H<sub>2</sub>, Raney Ni, EtOH; ix, BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C–room temp.; x, 2 M HCl, THF, 60 °C; xi, NaIO<sub>4</sub>, NaHCO<sub>3</sub>, acetone–water (5:1), room temp.; xii, Ph<sub>3</sub>P=CHC(O)Bu<sup>n</sup>, acetonitrile, room temp.; xiii, H<sub>2</sub>, Pd(OH)<sub>2</sub>, EtOH; xiv, Zn, sat. HCl/ether, 0 °C–room temp.

submitted to periodate oxidation (NaIO<sub>4</sub>, NaHCO<sub>3</sub>, acetone–water) to afford the hemiacetal aldehyde (**13**), which existed predominantly as its hydrate form (**13b**). Without isolation, (**13**) was then treated with Wittig reagent [Ph<sub>3</sub>P=CHC(O)–Bu<sup>n</sup>]<sup>12</sup> in acetonitrile to give the hemiacetal (**14**)† in 71% yield from (**11**) as a 5:1 mixture of *E*- and *Z*-isomers. Saturation of the double bond in (**14**) gave compound (**15**)† quantitatively, which was then oxidized with PCC to afford the bislactone (**16**) in 68% yield. Finally, reduction of the ketone carbonyl group in compound (**16**) was successfully achieved by modified Clemmensen reaction<sup>13</sup> which had been used by Yoshikoshi *et al.* for their synthesis of racemic avenaciolide,<sup>14</sup> to give the known precursor of (–)-isoavenaciolide (**17**)<sup>5–7</sup> in 81% yield. The physical and spectral properties of the synthetic (**17**) were in good accordance with those of an authentic sample<sup>7</sup> {m.p. 109–111 °C, [α]<sub>D</sub><sup>20</sup> –18° (c 1, CHCl<sub>3</sub>); lit.<sup>7</sup> m.p. 109–111 °C, [α]<sub>D</sub><sup>25</sup> –21° (c 1, CHCl<sub>3</sub>)}.

This synthesis shows that quebrachitol should be a useful starting material for the synthesis of enantiomerically pure natural products.

We thank Dr. K. Suzuki (Department of Chemistry, this University) for the spectra of compound (**17**) and helpful discussions, Professor A. Yoshikoshi and Dr. F. Kido (Tohoku University, Japan) for information about the modified Clemmensen reaction, and Yokohama Rubber Co., Ltd. (Tokyo, Japan) for quebrachitol.

Received, 20th March 1990; Com. 0/01222J

## References

- S. Hanessian, "Total Synthesis of Natural Products: The 'Chiron' Approach," Pergamon Press, Oxford, 1983.
- N. Chida, Y. Furuno, and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 1989, 1230; N. Chida, E. Yamada, and S. Ogawa, *J. Carbohydr. Chem.*, 1988, **7**, 555, and references cited therein.
- D. C. Aldridge and W. B. Turner, *J. Chem. Soc. C*, 1971, 2431.
- K. Yamada, M. Kato, M. Iyoda, and Y. Hirata, *J. Chem. Soc., Chem. Commun.*, 1973, 499; R. E. Damon, and R. H. Schlessinger, *Tetrahedron Lett.*, 1975, 4551; S. D. Burke, G. J. Pacofsky, and A. D. Piscopio, *ibid.*, 1986, **27**, 3345.
- R. C. Anderson and B. Fraser-Reid, *J. Org. Chem.*, 1985, **50**, 4781.
- C. E. McDonald and R. W. Dugger, *Tetrahedron Lett.*, 1988, **29**, 2413.
- K. Suzuki, M. Miyazawa, M. Shimazaki, and G. Tsuchihashi, *Tetrahedron*, 1988, **44**, 4061.
- J. van Alphen, *Ind. Eng. Chem.*, 1951, **43**, 141.
- N. Chida, M. Suzuki, M. Suwama, and S. Ogawa, *J. Carbohydr. Chem.*, 1989, **8**, 319.
- H. Paulsen and F. R. Heiker, *Liebigs Ann. Chem.*, 1981, 2180; H. Paulsen and W. von Deyn, *ibid.*, 1987, 133.
- E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
- M. Sakakibara and M. Matsui, *Agric. Biol. Chem.*, 1973, **37**, 1131.
- M. Toda, Y. Hirata, and S. Yamamura, *J. Chem. Soc., Chem. Commun.*, 1969, 919.
- F. Kido, Y. Tooyama, Y. Noda, and A. Yoshikoshi, *Chem. Lett.*, 1983, 881.

† The anomeric configurations in compounds (**14**) and (**15**) were specific and assumed to be β-OH from their <sup>1</sup>H NMR spectra (*J*<sub>4,5</sub> < 1.5 Hz).