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Total Synthesis of (±)-Trachyspic Acid and Determination of the Relative Configuration

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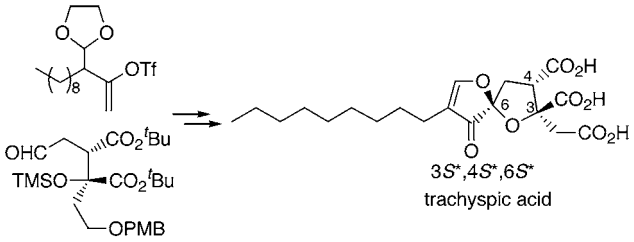
ABSTRACT



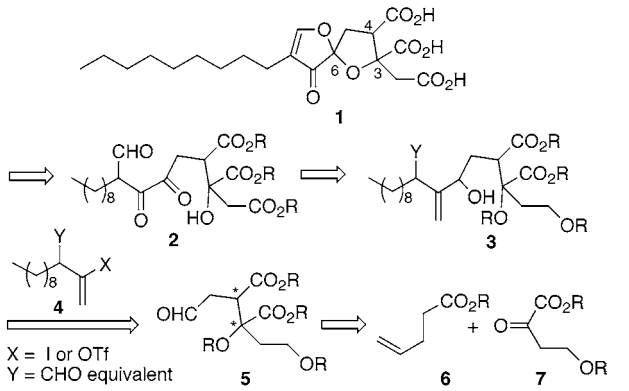
The first total synthesis of (±)-trachyspic acid, a tumor cell heparanase inhibitor, was accomplished based on Cr(II)/Ni(II)-mediated reaction of the aldehyde containing the citric acid moiety and the long-chain triflate, and the relative configuration of this natural product was determined.

Heparanase is known to participate in both tumor invasion and angiogenesis, suggesting its inhibition as a potential target for discovering novel drugs of cancer chemotherapy.[1] Trachyspic acid (**1**) was isolated from the culture broth of *Talaromyces trachyspermus* SANK 12191 after screening for substances that exhibit heparanase inhibitory activity.[2] Structurally, this compound is characterized by a novel spiroketal structure consisting of the 4-nonyl-3-furanone and the tetrahydrofuran containing a citric acid unit. The planar structure was determined by detailed NMR analysis; however, even the relative configuration was not elucidated. We now describe the first synthesis of (±)-trachyspic acid, thereby establishing its relative configuration to be 3*S**,4*S**,6*S**.

We envisaged that α-diketone aldehyde **2**, a precursor of **1**, could be accessed from aldehyde **5** via its Cr(II)/Ni(II)-mediated Nozaki−Hiyama−Kishi reaction[3,4] with **4** producing **3**. To access aldehyde **5** we selected aldol reaction of 4-pentenoate ester **6** with α-keto ester **7** because both (3*R**,4*S**)- and (3*S**,4*S**)-isomers were required for the determination of the relative stereochemistry of **1**.

The required α-keto ester **8** and triflate **9**, corresponding to **7** and **4**, respectively, were prepared as illustrated in Schemes 2[5] and 3[6].

Scheme 1. Retrosynthetic Analysis of Trachyspic Acid



(1) (a) Nakajima, M.; Irimura, T.; Di Ferrante, D.; Di Ferrante, N.; Nicolson, G. L. *J. Biol. Chem.* **1984**, *259*, 2283−2290. (b) Vlodavsky, I.; Korner, G.; Ishai-Michaeli, R.; Bashkin, P.; Bar-Shavit, R.; Fuks, Z. *Cancer Metastasis Rev.* **1990**, *9*, 203−226.

(2) Shiozawa, H.; Takahashi, M.; Takatsu, T.; Kinoshita, T.; Tanzawa, K.; Hosoya, T.; Furuya, K.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 357−369.

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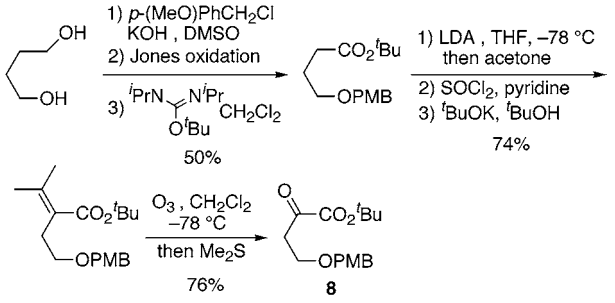
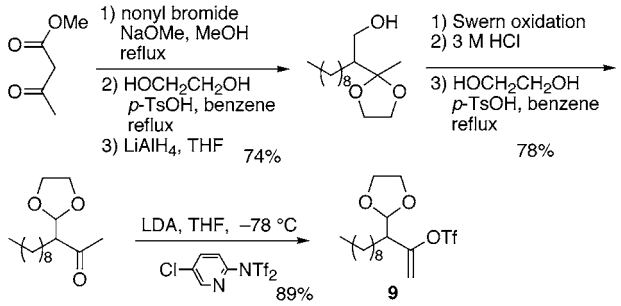
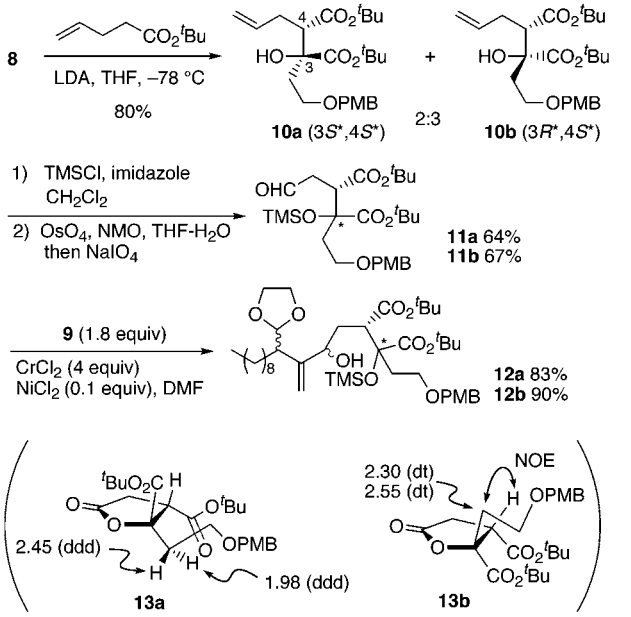
Scheme 2. Synthesis of α-Keto Ester **8**[7]



Scheme 3. Synthesis of Triflate **9**[8]



Scheme 4. Cr(II)/Ni(II)-Mediated Coupling



Aldol reaction of **8** and the lithium enolate generated from *tert*-butyl 4-pentenoate gave a 2:3 mixture of (3*S**,4*S**)-**10a** and (3*R**,4*S**)-**10b**, which were separated by column chromatography on silica gel. The stereochemistry of **10a** and **10b** was determined by ^{1}H NMR analysis and NOE experiments of the corresponding γ-lactones **13a** and **13b** prepared via osmylation, $NaIO_4$-oxidation, and PDC-oxidation. Upon silylation and oxidative cleavage of the olefin, **10a** and **10b** were converted to key aldehydes **11a** and **11b**, respectively. After experimentation under various conditions,[9,10] the optimum conditions to achieve the crucial Cr(II)/Ni(II)-mediated coupling reaction were found. Thus, when **11a** was reacted with triflate **9** in the presence of 4 equiv of $CrCl_2$ and 0.1 equiv of $NiCl_2$ in DMF at room temperature, the coupling reaction occurred very successfully to produce adduct **12a** in 83% yield. Similarly, adduct **12b** was obtained from **11b** in 90% yield. After Swern oxidation of **12a** followed by desilylation, treatment of **14a** with 3 M $HClO_4$ in THF at room temperature gave spiroketal **15a** as a diastereoisomeric mixture in good yield. When dilute HCl or *p*-TsOH was used as an acid catalyst, the spiroketal-formation required higher temperature and longer reaction time, leading to moderate yields of **15a** (30−60%). Treatment of **15a** with methanesulfonyl chloride in pyridine afforded diene **20a** as a 4:1 epimeric mixture, NOE measurement of which allowed us to determine the stereochemistry of the spirocenter of the major isomer to be *S**. Interestingly, dehydration of **15b** obtained from **12b** also produced **20b** as a major constituent of a 4:1 epimeric mixture. The predominant formation of the *S**-spirocenter observed in both cases can be interpreted by assuming oxonium ion intermediate **21** where the cyclization would occur from the less-hindered top face regardless of the C3-stereochemistry.

Upon acetylation and oxidative removal of the *p*-methoxybenzyl protecting group, **15a** gave alcohol **16a**, which was then converted to carboxylic acid **17a** by Dess−Martin oxidation[11] followed by $NaClO_2$-oxidation.[12] Finally, ozonolysis of **17a** and exposure of the resulting ketone to TFA furnished tricarboxylic acid **18a**. Similarly, tricarboxylic acid **18b** was synthesized from **15b** via **16b** and **17b**. At this stage, we found that **18a** was identical with trachyspic acid[2] by ^{1}H and ^{13}C NMR comparison. The trimethyl ester of **18a** also exhibited spectral properties in accord with those reported[2] for the trimethyl ester of natural trachyspic acid. Furthermore,

(3) (a) Takai, K.; Kimura, K.; Kuroda, T. Hiyama, T.; Nozaki, H. *Tetrahedron. Lett.* **1983**, *24*, 5281−5284. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048−6050. (c) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646.

(4) For a review see: Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 1, Chapter 1.6.4, pp 193−201.

(5) After aldol reaction with acetone, dehydration gave β,γ-unsaturated ester almost exclusively.

(6) The triflation reaction proceeded with perfect regioselectivity.

(7) For the esterification step see: Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261−2266.

(8) For the triflation step see: Commins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

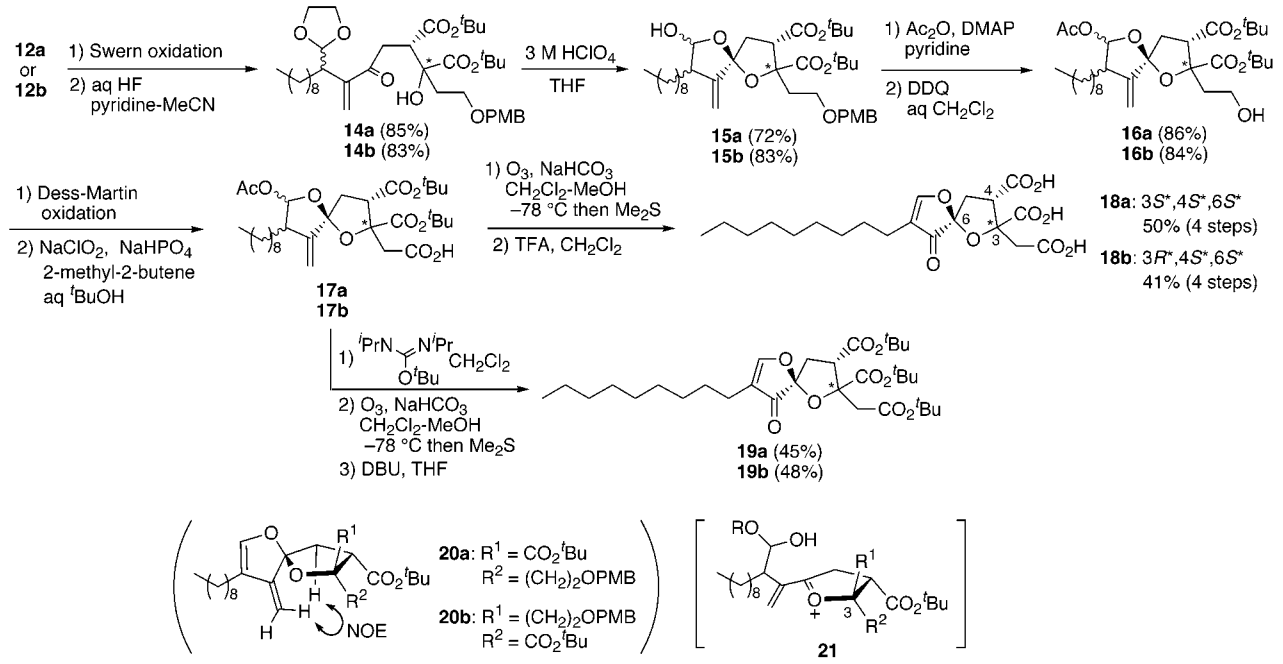
(9) In this particular case, use of 4-*tert*-butylpyridine as an additive turned out to decrease the yield of the coupling product (<60%). For the procedure with 4-*tert*-butylpyridine see: Sheng, D. P. X. C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6355−6358.

(10) When DMSO was used as a solvent, the coupling reaction became very sluggish.

(11) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(12) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.

Scheme 5. Completion of the Synthesis of Trachyspic Acid



tri-*tert*-butyl esters **19a** and **19b** were prepared from **17a** and **17b**, respectively, via esterification, ozonolysis, and elimination without employing acidic conditions. As a result, **19a** turned out to be completely identical with the tri-*tert*-butyl ester derived from **18a** with use of *N*,*N*-diisopropyl-*O*-*tert*-butylisourea. Since isomerization of the spirocenter is not likely to happen during these nonacidic transformations, this result allowed us to conclude unambiguously that the relative configuration of trachyspic acid is 3*S**,4*S**,6*S**.

In conclusion, we have achieved a convergent synthesis of (±)-trachyspic acid based on Cr(II)/Ni(II)-mediated Nozaki−Hiyama−Kishi reaction of the C1−C6 aldehyde containing the citric acid moiety and the C7−C18 long-chain triflate. Importantly, the relative configuration of the natural product has also been established for the first time. To determine the absolute structure, an enantioselective synthesis of trachyspic acid is under investigation.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, and ^{1}H and ^{13}C NMR spectra of trachyspic acid, 3-epitrachyspic acid, and their methyl esters. This material is available free of charge via the Internet at http://pubs.acs.org.

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