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Enantioselective formal total synthesis of (−)-trachyspic acid

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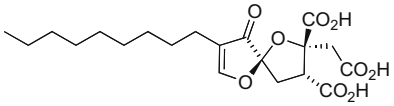
ABSTRACT

An enantioselective formal total synthesis of (−)-trachyspic acid was carried out using, as key steps, an asymmetric aldol reaction of a chiral oxazolidinone and a diastereoselective alkylation of a chiral 1,3-dioxolan-2-one. The key lactone **3** was synthesized in five steps starting from dioxolanone **9**.

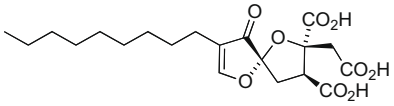
Trachyspic acid was isolated from the culture broth of *Talaromyces trachyspermus* SANK 12191 and was identified as a potent inhibitor of heparanase with an IC_{50} of 36 μM. Structurally, this compound is characterized as a spiroketal consisting of a 4-nonyl-3-furanone and of a tetrahydrofuran containing a citric acid unit (Fig. 1).

The Hatakeyama group first reported its structure and relative stereochemistry.[1] Subsequently, Rizzacasa et al. reported the first enantioselective total synthesis of (−)-trachyspic acid (**1**) via lactone **3** (Scheme 1), which led to the determination of the absolute stereochemistry of the natural product as the antipode **2**.[2,3]

Recently, we reported an enantioselective total synthesis of citrafungin A using dioxolanone **9**,[4] and we have now extended the methodology to the formal total synthesis of (−)-trachyspic acid (**1**) by making key Rizzacasa lactone **3**. As described in full in our synthesis of citrafungin A, dioxolanone **9** was prepared in eight steps starting from commercially available 4-(benzyloxy)butyric acid using, as key steps, an Evans aldol reaction[5] of oxazolidinone **6** to **7** and a stereoselective Seebach enolate self-regeneration of stereochemistry alkylation of **8** with *t*-butyl bromoacetate (Scheme 2).[6]

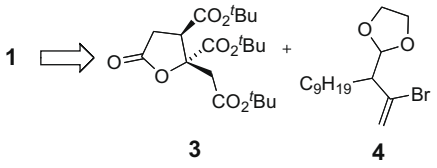


(-)-(3*R*,4*R*,6*R*)-trachypsic acid (**1**)



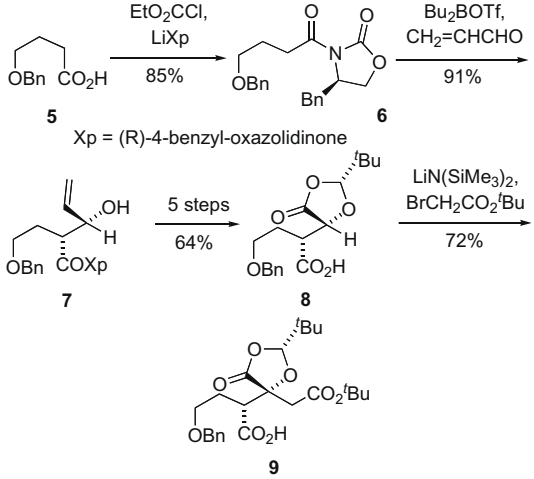
(+)-(3*S*,4*S*,6*S*)-trachypsic acid (**2**)

Figure 1. Structures of (−)-trachyspic acid (**1**) and (+)-trachyspic acid (**2**).



Scheme 1. Rizzacasa approach to (−)-trachyspic acid (**1**).

Hydrogenolysis of benzyl ether **9** followed by acid catalyzed cyclization gave lactone **10** as a white solid (Scheme 3), the structure of which was confirmed by an X-ray structure determination (Fig. 2).[7]



Scheme 2. Key steps in the synthesis of dioxolanone **9**.[4]

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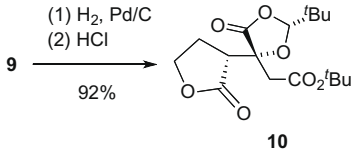


Scheme 3. Synthesis of lactone **10**.

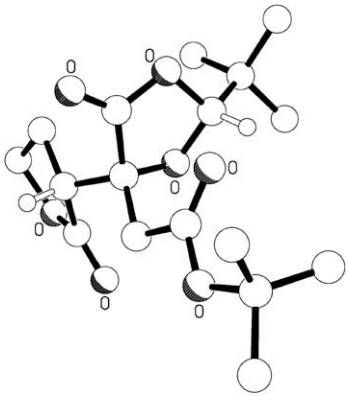
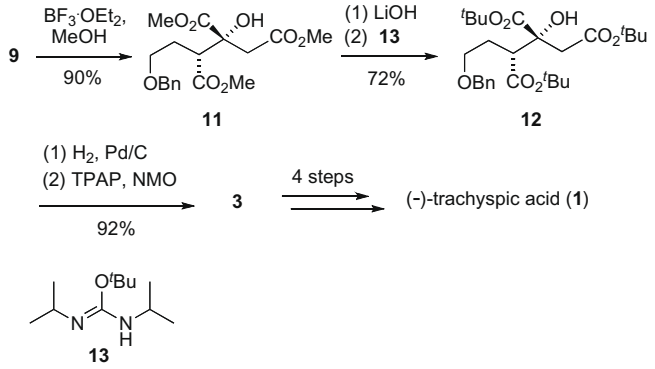


Figure 2. X-ray crystallographic ORTEP structure of lactone **10**.



Scheme 4. Synthesis of key lactone **3**.

Alternatively, dioxolanone **9** was smoothly ring-opened using boron trifluoride diethyl etherate in methanol at reflux in a sealed tube,[8] which gave the triester **11** (Scheme 4). Lithium hydroxide-mediated saponification gave the corresponding tricarboxylic acid, which was directly re-esterified using freshly prepared *N*,*N*′-di-isopropyl-*O*-*t*-butylisourea (**13**) to afford tri-*tert*-butyl ester **12** in 72% yield over the two steps. Sequential benzyl ether hydrogenolysis and tetrapropylammonium perruthenate (TPAP) oxidation[9] of **12** gave lactone **3** in 92% yield over the two steps.

Lactone **3** showed data identical[10] to those reported by the Rizzacasa group,[2,3] and this was confirmed by redetermining its X-ray crystallographic structure (see Supplementary data). In summary, we have reported the formal total synthesis of (−)-trachyspic acid (**1**) using an Evans aldol reaction and a Seebach dioxolanone alkylation. The synthesis of lactone **3** was achieved in 21% yield over 13 steps.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.057.

References and notes

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7. Crystal data for **10**: $C_{17}H_{26}O_7$, M = 342.38, orthorhombic, $P2_12_12_1$ (no. 19), a = 5.94340(11), b = 13.4581(3), c = 22.8780(4) Å, V = 1829.94(6) Å^3, Z = 4, D_c = 1.243 g cm^{-3}, μ(Mo-Kα) = 0.096 mm^{-1}, T = 173 K, colorless block needles, Oxford Diffraction Xcalibur 3 diffractometer; 6146 independent measured reflections, F^2 refinement, R_1 = 0.037, wR_2 = 0.080, 3909 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 65°], 217 parameters. The absolute structure of **10** could not be determined by either R-factor tests [$R_1^+ = 0.0366$, $R_1^- = 0.0366$] or by use of the Flack parameter [x^+ = +0.0(6), x^- = +1.0(6)], and so it was assigned based on the known stereochemistry at C(6). CCDC 704898.
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9. Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13–19.
10. Analytical data for lactone **3**: $[\alpha]_D^{25}$ −15.1 (*c* 1, CH_2Cl_2); IR (KBr) 1803, 1735, 1369, 1251, 1147, 1066, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (dd, *J* = 8.6, 3.8 Hz, 1H), 3.08 (d, *J* = 17.3 Hz, 1H), 2.88 (d, *J* = 17.3 Hz, 1H), 2.84 (dd, *J* = 17.8, 8.3 Hz, 1H), 2.76 (dd, *J* = 17.5, 3.8 Hz, 1H), 1.49 (s, 9H), 1.48 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 169.0, 168.3, 167.7, 83.7, 83.2, 82.0, 47.6, 39.0, 32.1, 28.0, 27.9, 27.7; HRMS (ESI) calcd for $C_{20}H_{32}O_8Na$: $(M+Na)^+$, 423.1995, found: $(M+Na)^+$, 423.2004.