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Asymmetric synthesis of (+)-trachyspic acid

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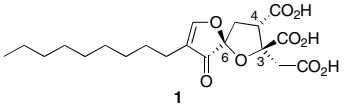
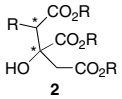
ABSTRACT

Aldol reaction of di-*tert*-butyl 4-(4-methoxybenzyloxy)-2-oxobutanoate with pent-4-enal using (*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(pyrrolidin-2-ylmethyl)thiourea hydrochloride as a catalyst, followed by Pinnick oxidation and *tert*-butyl esterification, gave (2*S*,3*S*)-di-*tert*-butyl 2-(2-(4-methoxybenzyloxy)ethyl)-3-allyl-2-hydroxysuccinate in high optical purity (85% ee), from which the total synthesis of (+)-trachyspic acid, a tumor cell heparanase inhibitor, was accomplished.

Trachyspic acid (**1**) was isolated from the culture broth of *Talaromyces trachyspermus* SANK 12191 as a potent inhibitor of heparanase with an IC_{50} of 36 μM.[1] Structurally, this compound is characterized by a novel spiroketal moiety consisting of the 4-nonyl-3-furanone and the tetrahydrofuran containing a citric acid unit. The two-dimensional structure was elucidated by NMR analysis and degradation experiments,[1] and the relative configuration was confirmed by our racemic synthesis.[2] Recently, Rizzacasa et al. unambiguously determined the absolute configuration to be 3*S*,4*S*,6*S* by the enantiospecific synthesis of both enantiomers from D-deoxyribose.[3] In connection with a project directed toward the synthesis of the alkyl citrate family of natural products such as viridiofungins[4] and citrafungins,[5] we were interested in developing an efficient enantioselective approach to a common alkyl citrate structure **2**. Herein, we report an asymmetric synthesis of (+)-trachyspic acid (**1**) employing an organocatalytic aldol reaction of an α-keto ester[6] with an aldehyde for the assembly of the alkyl citrate core.



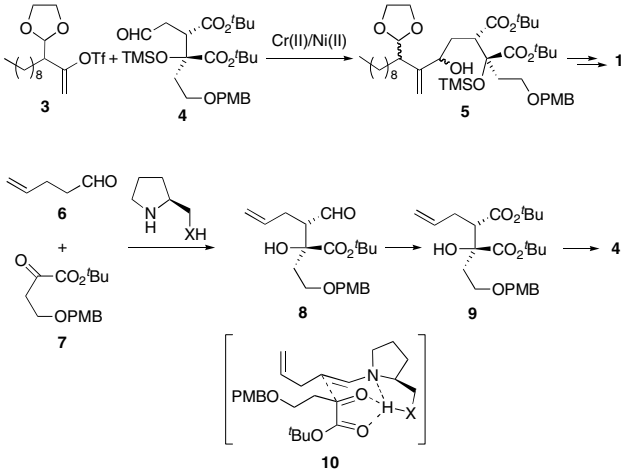
1



2

We have developed an effective methodology for the synthesis of **1** via Cr(II)/Ni(II)-mediated Nozaki–Hiyama–Kishi reaction[7] of triflate **3** and aldehyde **4**, an alkyl citrate core, giving **5** in the racemic synthesis.[2] We therefore focused on the enantioselective preparation of aldehyde **4** for the synthesis of (+)-trachyspic acid (**1**). To expeditiously access **4**, we envisaged asymmetric aldol reaction of pent-4-enal (**6**) and α-keto ester **7** under chiral proline-based catalysis[8] (Scheme 1). We expected that this aldol reaction would preferentially proceed through six-membered chairlike transition state **10** locked by hydrogen bonding to produce diastereomer **8**, convertible to **4** via **9**.

Before we examined the key organocatalytic aldol reaction, we prepared (2*S*,3*S*)-diester **9** by a reliable route (Scheme 2). The synthesis started from compound **11** which had been used for the synthesis of virigiofungin A.[4b] Thus, protection of **11** as its TIPS ether followed by selective removal of the THP protecting group afforded alcohol **12**, which was subjected to Katsuki–Sharpless asymmetric epoxidation[9] to produce epoxide **13** in 88% ee. Nucleophilic opening of **13** with allylmagnesium chloride proceeded with excellent regio- and stereoselectivity to give diol **14** quantitatively. It is important to note that the use of allylmagnesium bromide in place



Scheme 1. Strategy leading to key intermediate **4**.

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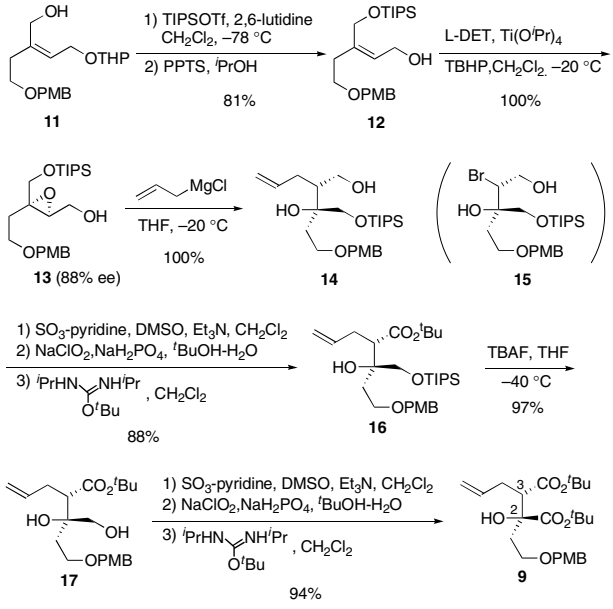
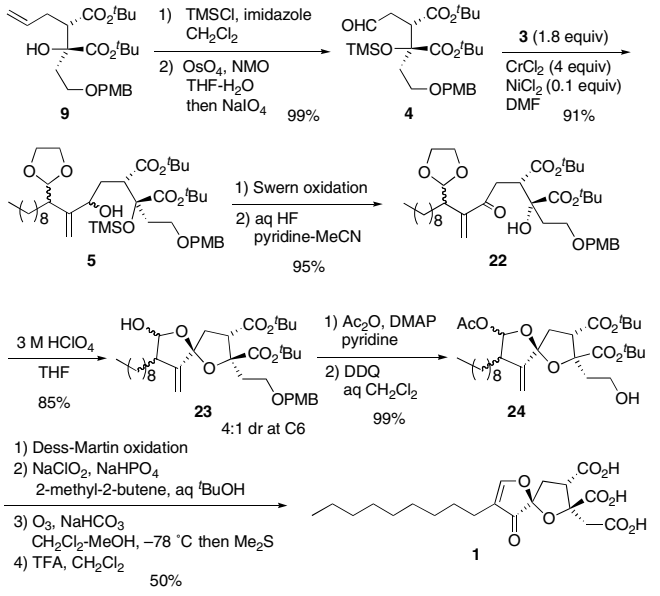


Scheme 2. Synthesis of (2*S*,3*S*)-diester **9** via a reliable route.

of allylmagnesium chloride provided bromide **15** as a major product. Upon successive Parikh–Doering oxidation,[10] Pinnick oxidation,[11] and esterification using *N*,*N*′-diisopropyl-*O*-2-*tert*-butylisourea,[12] **14** afforded **16** in good overall yield. After desilylation of **16**, diol **17** was converted to (2*S*,3*S*)-diester **9**[13] by the same procedure as employed for the transformation of **14** to **16**.

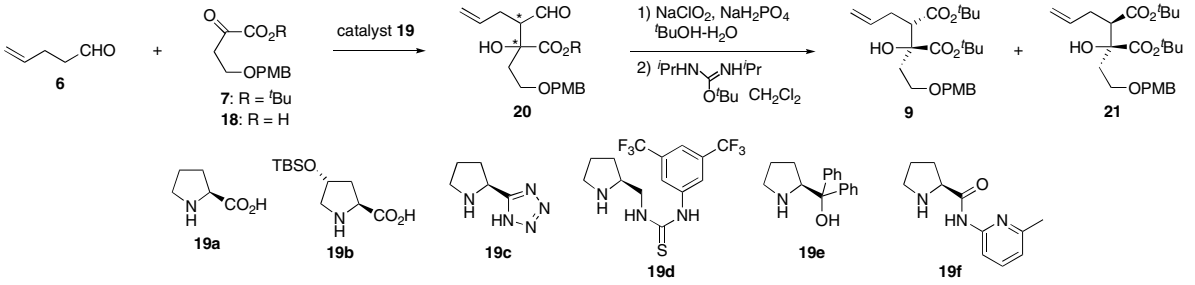
With an authentic sample of (2*S*,3*S*)-diester **9** in hand, we then investigated aldol reaction of aldehyde **6** with α-keto ester **7** or α-keto acid **18** under various conditions using L-proline and five other catalysts (Table 1). The reactions were evaluated by HPLC analysis using a chiral column after converting the aldol products **20** to the corresponding di-*tert*-butyl esters by Pinnick oxidation followed by esterification. When the reaction was carried out using 0.5 equiv of L-proline **19a** in toluene at room temperature for 21 h, (2*S*,3*S*)-isomer **9** (61% ee) and (2*S*,3*R*)-isomer **21** (19% ee)[14] were obtained in a ratio of 2:3 in 46% total yield from **7** (entry 1). This proline-catalyzed reaction turned out to be very low yielding in DMSO, DMF, and CH_2Cl_2. (4*R*)-4-TBSO-L-proline **19b**[15] gave a comparable result to that obtained by the proline-catalyzed reaction (entry 2). Either **19c**[16] or **19d**[17] brought about poorer diastereo- and enantioselectivity (entries 3 and 4). However, it is gratifying to find that the use of the hydrochloride of **19d** (**19d**·HCl) markedly improved the enantio- and diastereoselectivity as well as chemical yield. Thus, when the reaction was carried out for 2 days, **9** (85% ee) and **21** (33% ee) were obtained in a ratio of 2:1 in 49% total yield from **7** (entry 5). Amino alcohol **19e** did not show any catalytic ability, and α-keto ester **7** was recovered in 95% yield even after 8 days. Furthermore, aldol reaction of **6** with α-keto acid **18** using basic catalyst **19f**[6d] was also examined under various conditions with expectation of stronger acid–base interaction leading to rate acceleration as well as high enantio- and diastereoselectivity. However, the results were not encouraging at all.

Following the procedure we established in the synthesis of racemic tracyspic acid,[2] the total synthesis of (+)-trachyspic acid was



Scheme 3. Completion of the total synthesis of (+)-trachyspic acid (**1**).

Table 1
Asymmetric aldol reaction of **6** and **7**[a]



Entry	Solvent	Catalyst	Time (h)	Yield (**9** + **21**)[b] (%)	Ratio (**9**:**21**)[c]	ee % of **9**[c]	ee % of **21**[c]
1	Toluene	**19a**	21	46	2:3	61	19
2	Toluene	**19b**	25	45	1:1	65	23
3	CH_2Cl_2	**19c**	68	29	1:1	41	0
4	DMF	**19d**	24	34	1:1	49	0
5	DMF	**19d**·HCl	48	49	2:1	85	33

[a] The reactions were conducted at room temperature using aldehyde **6** (3 equiv), α-ketoester **7** (1 equiv), and catalyst **19** (0.5 equiv).
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral column.

accomplished from (2*S*,3*S*)-diester **9** as illustrated in Scheme 3. Thus, **9** was first converted to aldehydes **4** by silylation followed by oxidative cleavage of the olefinic double bound. Upon reaction of **4** with triflate **3** 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 cleanly to produce alcohol **5** in good yield. After Swern oxidation of **5** followed by desilylation, exposure of **22** to 3 M $HClO_4$ in THF at room temperature promoted spiroacetalization to give spiroacetal **23** as a diastereoisomeric mixture in good yield. In this case, the C6 spirocenter was preferentially formed in *S* configuration (dr = 4:1).[18] Upon acetylation and oxidative removal of the *p*-methoxybenzyl protecting group, **23** gave alcohol **24**. Finally, (+)-trachyspic acid (**1**)[19] was successfully obtained from **24** by four-step sequence involving Dess–Martin oxidation, Pinnick oxidation, ozonolysis, and treatment with TFA. The specific rotation and spectroscopic properties (^{1}H and ^{13}C NMR) were in good agreement with those of natural trachyspic acid.

In conclusion, although there still remain the selectivity issues to be improved in the key organocatalytic aldol reaction, we have developed a concise enantioselective approach to an alkyl citrate structure and successfully achieved a total synthesis of (+)-trachyspic acid via Cr(II)/Ni(II)-mediated Nozaki–Hiyama–Kishi coupling of the alkyl citrate moiety and the long chain triflate.

Acknowledgment

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13. $[\alpha]_D^{25}$ +10.5 (*c* 0.780, $CHCl_3$) (88% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.45 (s, 9H), 1.93 (dt, *J* = 13.2, 6.2 Hz, 1H), 2.08 (m, 1H), 2.17 (dt, *J* = 13.5, 6.6 Hz, 1H), 2.46 (ddd, *J* = 6.7, 12.0, 15.0 Hz, 1H), 2.68 (dd, *J* = 2.7, 11.7 Hz, 1H), 3.50 (dt, *J* = 2.1, 6.3 Hz, 2H), 3.79 (s, 3H), 4.37 (dd, *J* = 11.4, 13.8 Hz, 2H), 4.49 (dd, *J* = 1.5, 12.3 Hz, 1H), 5.05 (dd, *J* = 1.2, 16.8 Hz, 1H), 5.72 (ddt, *J* = 9.3, 16.5, 6.3 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.0, 28.1, 32.2, 37.2, 54.1, 55.3, 65.5, 72.9, 76.6, 81.4, 82.9, 113.8, 116.8, 129.6, 130.2, 135.5, 159.3, 171.7, 173.2; FTIR (neat) 3779, 2712, 3480, 2971, 1722, 1594, 1249, 1157, 840 cm^{-1}; MS (EI) *m*/*z* 44, 57, 121 (100), 137, 201, 393, 450 (M^+); HRMS (EI) calcd for $C_{21}H_{29}O_5$ [$(M-{}^tBu)^+$]: 393.1913, found, 393.2060.
14. The absolute configuration was deduced from the fact that treatment of **21** with LDA in THF at −40 °C followed by aq NH_4Cl gave **9** and **21** in a ratio of 1:9 in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (18H, s), 1.97 (1H, dt, *J* = 7.5, 14.1 Hz), 2.13 (1H, ddd, *J* = 5.7, 7.8, 13.5 Hz), 2.42 (2H, m), 2.66 (1H, dd, *J* = 4.2, 10.2 Hz), 3.48 (1H, ddd, *J* = 7.5, 9.0, 16.5 Hz), 3.56 (1H, dt, *J* = 5.4, 9.0 Hz), 3.78 (3H, s), 4.38 (2H, d, *J* = 3.3 Hz), 5.00 (1H, d, *J* = 10.2 Hz), 5.06 (1H, dd, *J* = 1.2, 16.8 Hz), 5.78 (1H, ddt, *J* = 7.2, 10.2, 14.1 Hz), 7.23 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 28.1, 31.4, 45.9, 53.0, 55.3, 65.4, 72.8, 76.0, 81.5, 82.6, 113.8, 116.9, 129.5, 130.3, 135.8, 159.2, 172.1, 173.6; FTIR (neat) 3498, 1724, 1573, 1612, 1514, 1458, 1392, 1367, 1248, 1149, 1036 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{38}O_7$ (M^+): 450.2617, found, 450.2625.
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18. Dehydration of **23** with methanesulfonyl chloride in pyridine afforded the corresponding diene as a 4:1 epimeric mixture. NOE measurement of this mixture allowed us to determine the configuration of the C6 spirocenter of the major isomer to be *S*.
19. $[\alpha]_D^{27}$ +4.9 (*c* 0.94, MeOH) [lit.[1] $[\alpha]_D^{25}$ +3.1 (*c* 1.00, MeOH)]; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, *J* = 7.0 Hz, 3H), 1.23 (br s, 12H), 1.38 (m, 2H), 2.02 (t, *J* = 8.0 Hz, 2H), 2.34 (m, 2H), 2.67 (d, *J* = 17.0 Hz, 1H), 2.85 (d, *J* = 16.5 Hz, 1H), 3.57 (dd, *J* = 8.0, 11.5 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 13.9, 20.4, 22.0, 27.5, 28.6, 28.6, 28.8, 31.2, 37.4, 38.7, 48.4, 86.5, 108.0, 116.7, 170.0, 170.5, 171.3, 174.4, 198.1; FTIR (neat) 3446, 2925, 2858, 2613, 1936, 1722, 1604, 1396, 1223, 1140, 1066, 1003 cm^{-1}; MS (FAB) *m*/*z* 41 (100), 435 [$(M+Na)^+$], 457 [$(M+2Na)^+$].