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Addition of Metallo Enolates to Chiral 1-Acylpyridinium Salts: Total Synthesis of (+)-Cannabisativine

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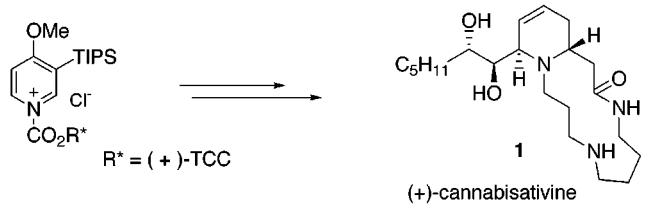
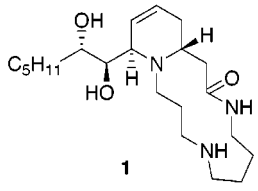
ABSTRACT



A novel route to the first asymmetric synthesis of (+)-cannabisativine (1) is described. The total synthesis of 1 was accomplished with a high degree of regio- and stereoselectivity in 19 steps and 9% overall yield.

The polyamine alkaloid (+)-cannabisativine **(1)** was isolated from *Cannabis sativa* L. in 1975, and its structure was determined by X-ray diffraction analysis.[1] Spurred by its unique architecture, synthetic efforts ensued and resulted in two racemic syntheses from the laboratories of Natsume[2] and Wasserman.[2b] A few years later, the absolute stereochemistry of **1** was established through the synthesis of (−)-cannabisativine by Hamada and co-workers.[3]



(+)-cannabisativine

Recently, we have been investigating the addition of metallo enolates to chiral 1-acylpyridinium salts.[4] This reaction is useful for the enantioselective preparation of 2-substituted piperidines containing functionality and stereocenters in the C-2 side chain. The piperidine core of cannabisativine, with its 1,2-diol side chain, appeared to be an attractive target for this methodology. Herein is described the first asymmetric synthesis of natural (+)-cannabisativine (**1**). The four stereocenters and the carbon−carbon double bond are introduced with a high degree of stereo- and regiochemical control.

The synthesis began as shown in Scheme 1. The enantiopure 1-acylpyridinium salt **2**[5] was treated with zinc enolate **3** to give dihydropyridone **4** in 85% yield.[6] Conversion of **4** to Weinreb's amide **5** proceeded in near quantitative yield.[4,7]

(1) (a) Lotter, H. L.; Abraham, D. J.; Turner, C. E.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *Tetrahedron Lett.* **1975**, *7*, 2815. (b) Turner, C. E.; Hsu, M.-F. H.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. L. *J. Pharm. Sci.* **1976**, *65*, 1084.

(2) (a) Ogawa, M.; Kuriya, N.; Natsume, M. *Tetrahedron Lett.* **1984**, *25*, 969. (b) Wasserman, H. H.; Leadbetter, M. R. *Tetrahedron Lett.* **1985**, *26*, 2241.

(3) Hamada, T.; Zenkoh, T.; Sato, H.; Yonemitsu, O. *Tetrahedron Lett.* **1991**, *32*, 1649.

(4) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2615 and references therein.

(5) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

(6) The yield is of diastereomerically pure **4** isolated by radial preparative layer chromatography. The reaction proceeded in >95% de; see ref 4.

(7) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685 and references therein.

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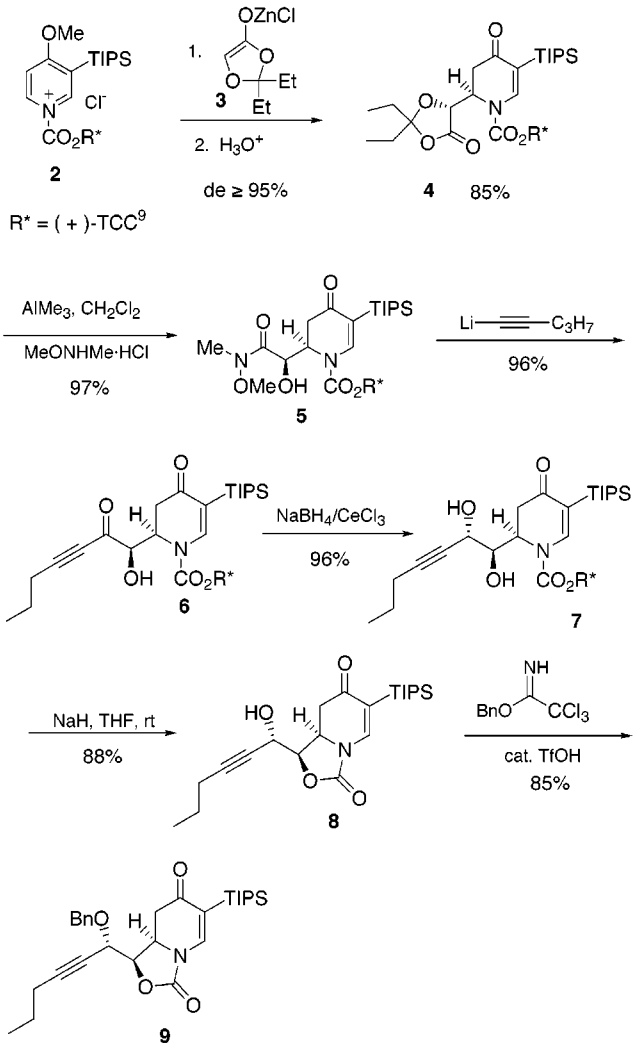
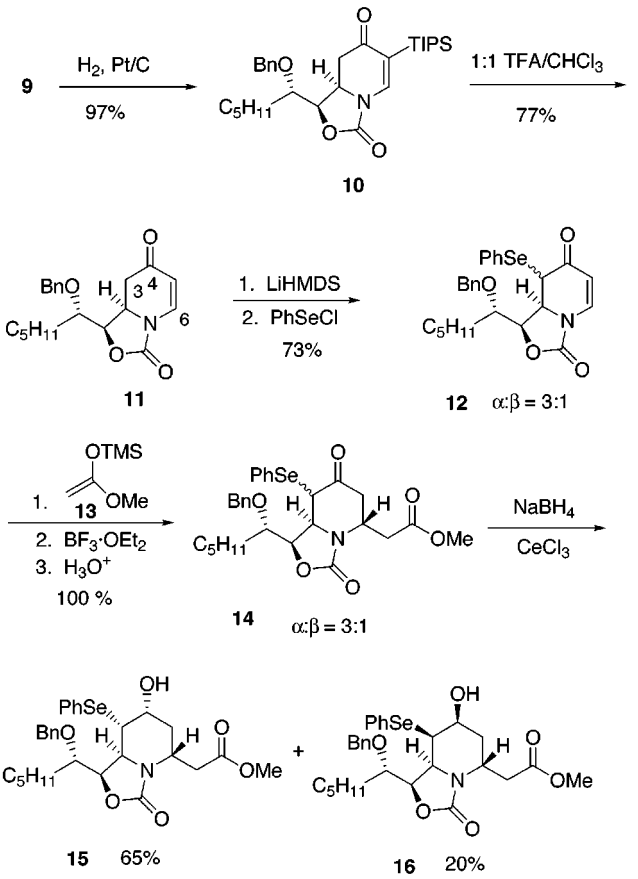
Scheme 1



reduction of the alkyne bond could be achieved via catalytic hydrogenation to give **10**. The TIPS group was now removed with TFA ($CHCl_3$, reflux, 12 h) to provide bicyclic carbamate **11** (Scheme 2). At this stage, an acetic acid unit needed to

Scheme 2



Addition of pentynyllithium (5 equiv) to **5** provided ketone **6**, which was reduced under Luche conditions to give diol **7** (>95% de) in excellent yield.[8] The previous three steps could be accomplished in high overall yield due to the C-5 TIPS group which protects the dihydropyridone against nucleophilic attack. On treatment of **7** with sodium hydride, cyclic carbamate **8** was formed and isolated in 88% yield. In addition, the released chiral auxiliary, (+)-TCC,[9] was recovered (94%). The remaining secondary hydroxyl group of **8** was protected as its benzyl ether using benzyl trichloroacetimidate to afford **9**.[10] With the TIPS group still protecting the enone system of dihydropyridone **9**, clean

be introduced stereoselectively at C-6 of **11**, and regiospecific incorporation of a C-3,4 olefin into the piperidine ring was required. Selenenylation of **11** via its enolate provided phenyl selenides **12** as a 3/1 mixture of diastereomers. A latent acetic acid unit was introduced at C-6 with complete stereoselectivity using a Mukaiyama−Michael reaction.[11] Addition of BF_3 etherate to a mixture of **12** and *O*-silyl ketene acetal **13**[12] (CH_2Cl_2, −78 °C, 30 min) followed by acidic workup afforded piperidones **14** in quantitative yield. Luche reduction of **14** gave an 85% crude yield of two alcohols, **15** and **16**, which were used directly as a mixture in the next step. A one-pot procedure was developed to convert crude **15**/**16** into the desired tetrahydropyridine **18** (Scheme 3). The crude mixture (**15**/**16**) in toluene was treated with 1,1′-thiocarbonyldiimidazole (DMAP, toluene, reflux, 8 h) to give the corresponding thiocarbamates **17**, which were reduced in situ on addition of Bu_3SnH/AIBN (reflux, 10 min) to afford tetrahydropyridine **18** in 85% overall yield.[11b] The ester **18** was converted to amide **20** via its acid chloride and amino alcohol **19**[13] using Schotten−Baumann conditions (NaOH, CH_2Cl_2, rt).

(8) This highly stereoselective reduction is likely a result of a chelation-controlled addition mechanism.

(9) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.

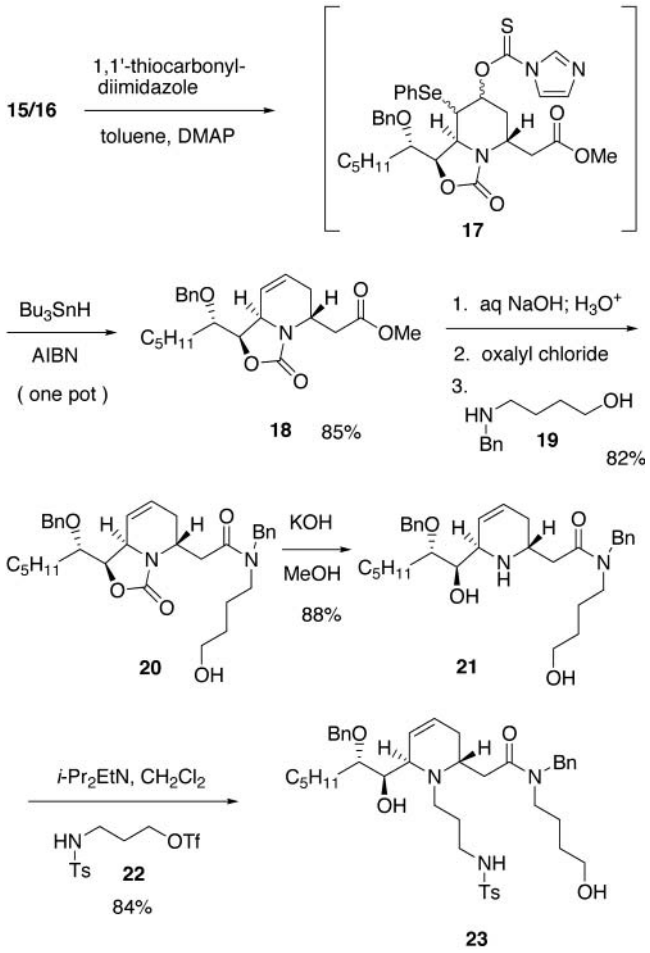
(10) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

(11) (a) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163. (b) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **1999**, *1*, 1031.

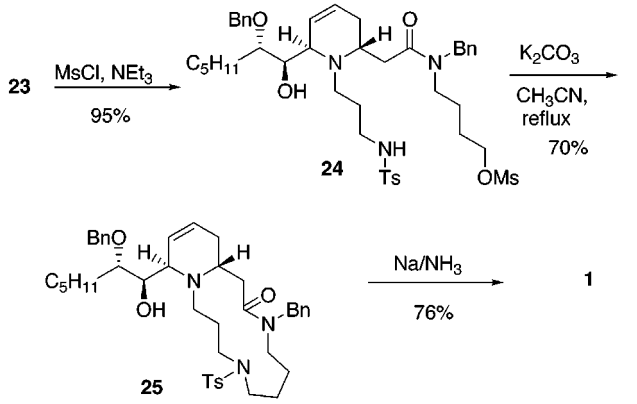
(12) The 1-methoxy-1-trimethylsiloxyethene (**13**) was prepared by a literature procedure: Collins, D. J.; Cullen, J. D. *Aust. J. Chem.* **1988**, *41*, 735.

(13) Lesher, G. Y.; Surrey, A. R. *J. Am. Chem. Soc.* **1955**, *77*, 636.

Scheme 3



Scheme 4



The oxazolidinone ring of **20** was opened in the presence of the tertiary amide group by treatment with refluxing aqueous KOH to provide aminodiol **21**.[14] The 13-membered lactam ring of **1** was constructed using a method similar to that reported by Weinreb for the synthesis of anhydrocannabisativene.[15] Treatment of **21** with triflate **22** (1.6 equiv) in the presence of Hunig's base afforded the tertiary amine **23**. After conversion to the primary mesylate **24** (Scheme 4), cyclization was carried out in acetonitrile/K_2CO_3 to provide lactam **25** in 70% yield.

Global deprotection using sodium in liquid ammonia gave a 76% yield of (+)-cannabisativine (**1**), which exhibited spectral data in agreement with reported data for authentic material.[2b] The melting point (165−66 °C) and optical rotation, $[\alpha]_D^{23}$ +51.8 (*c* 0.425, $CHCl_3$), were also in agreement with the literature values [mp 167−68 °C; $[\alpha]_D$ +55.1 (c 0.53, $CHCl_3$)].[1a]

In summary, the first asymmetric synthesis of (+)-cannabisativine (**1**) has been accomplished in 19 steps with a high degree of stereocontrol. Key to the success of this total synthesis was the metallo enolate addition to chiral acylpyridinium salt **2**. This allowed the preparation of dihydropyridone building block **4** which contains two contiguous stereocenters of the right absolute stereochemistry for the natural product target. The conversion of dihydropyridone **7** to bicyclic carbamate **8** was also of strategic importance. In one step, one secondary alcohol was protected, the chiral auxiliary was released, and a bicyclic system was formed with the proper conformational bias to allow the last stereocenter to be introduced with complete control of stereochemistry. This strategy should be useful for the enantioselective preparation of other complex alkaloids. Efforts in this direction are ongoing in our laboratories.

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Supporting Information Available: Characterization data for compounds **4**−**12**, **14**−**16**, **18**, **20**−**21**, **23**−**25**, and **1**, ^{1}H and ^{13}C NMR spectra of **6**−**10**, **12**, **14**−**16**, **18**, **20**−**21**, **23**−**25**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0056271

(14) The corresponding secondary amide suffers significant hydrolysis under these conditions.

(15) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.