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First Enantioselective Total Synthesis of (+)-(*R*)-Pinnatolide Using an Asymmetric Domino Allylation Reaction

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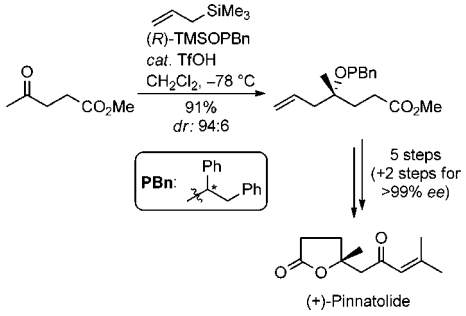
ABSTRACT



An efficient total synthesis of (+)-(*R*)-Pinnatolide is described. As a key step an asymmetric multicomponent domino allylation reaction of methyl levulinate is used to form the quaternary stereogenic center in a highly selective way.

In 1991, Bohlmann et al. isolated the isoprenoide Pinnatolide (**1**) from the aerial parts of the *Athanasia* species, e.g. *A. pinnata* or *A. crithmifolia*, and determined its constitution, however without giving the absolute configuration of the stereogenic center (Figure 1).[1] Unfortunately, neither the optical rotation nor a CD spectrum of the natural product is available.

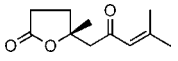


Figure 1. (+)-(*R*)-Pinnatolide (**1**).

Here we describe the first stereoselective synthesis of (+)-(*R*)-Pinnatolide (**1**) using the auxiliary mediated multicomponent domino allylation reaction of aliphatic methyl ketones developed in our group.[2]

The asymmetric allylation of ketones is still an important field of research.[3] Whereas several selective methods for aryl and α,β-unsaturated alkyl ketones are known,[4] for the allylation of saturated alkyl ketones our procedure is still the only one which gives high selectivities with the advantage of forming the corresponding ethers of the obtained tertiary alcohols in a domino process with a benzyl protecting group. As starting material for the synthesis of **1** the commercially available methyl levulinate (**2**) and the trimethylsilyl ether of (*R*)-phenylbenzylcarbinol[5] (**4**) as a chiral inductor were employed. The new auxiliary **4** has several advantages over the norpseudoephedrine derived auxiliary[6] which has been previously used by us. Thus, it can easily be obtained via an enantioselective reduction of

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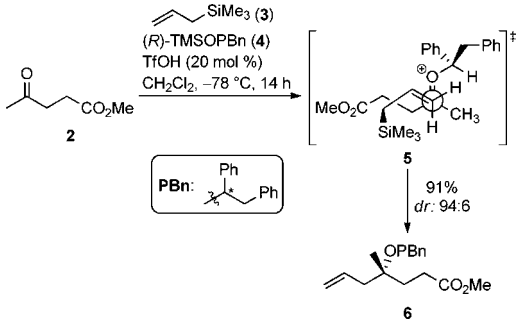
benzylphenylketone, and the phenylbenzyl moiety in the allylation product is an excellent protecting group, which can be removed either by hydrogenolysis or under Birch conditions.[7] In the Supporting Information an improved procedure is described for the synthesis of **4** with an enantiomeric excess of >99%.

Scheme 1. Asymmetric Multicomponent Allylation Reaction

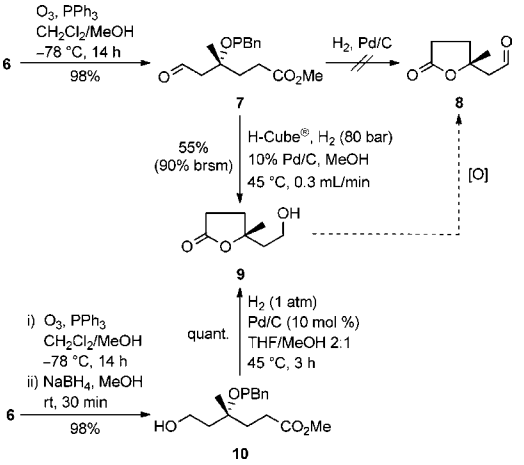


Treatment of **2** with allyltrimethylsilane (**3**) in the presence of the auxiliary **4** (>99% *ee*) and catalytic amounts of triflic acid in dichloromethane at −78 °C afforded the homoallylic ether (*R*,*R*)-**6** in 91% yield with a diastereoselectivity of 94:6 (Scheme 1).

The reaction proceeds via an intermediary formed oxeniumion which is favorably attacked by the allylsilane **3** from the *si*-face.[8] Exemplarily, the most favored synclinal transition state **5** is shown in Scheme 1. The well-established inducing effect of the auxiliary **4** can be explained by the higher steric demand of the phenyl group compared to the benzyl group.

As the next step in the synthesis of **1**, a mixture of the homoallylic ether (*R*,*R*)-**6** and its minor epimer was ozonolyzed at −78 °C in dichloromethane/methanol (10:1) with triphenylphosphin as a peroxide scavenger to afford the corresponding diastereomeric mixture of aldehyde **7** in 98% yield. However, hydrogenolytic deprotection of **7** using the H-Cube with 10% palladium on a charcoal cartridge as the catalyst, a hydrogen pressure of 80 bar, and methanol as the solvent at 45 °C gave not the desired γ-lactone aldehyde (*R*)-**8** but the γ-lactone alcohol (*R*)-**9**.[9] Though **9** can easily be transformed into **8** by oxidation, the obtained isolated yield of 55% in the deprotection step was not satisfactory (Scheme 2).

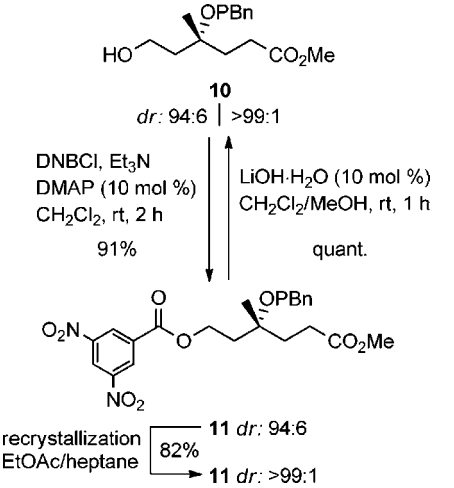
Scheme 2. Deprotection by Using Hydrogenolysis



We therefore performed a reductive workup of the mixture obtained by ozonolysis of **6** and its epimer using sodium borohydride in methanol to afford the alcohol (*R*,*R*)-**10** together with its isomer in 98% yield (*dr* 94:6). Since the mixture of epimers could not be separated by chromatography, the dinitrobenzoates were prepared using 3,5-dinitrobenzoyl chloride (DNBCl), triethylamine, and catalytic amounts of *N*,*N*-dimethylaminopyridine (DMAP) in dichloromethane at ambient temperature. Recrystallization afforded (*R*,*R*)-**11** in 82% yield as a single stereoisomer (Scheme 3). Furthermore, the absolute configuration of (*R*,*R*)-**11** could be confirmed by single crystal X-ray analysis.[10]

Solvolysis of (*R*,*R*)-**11** in a dichloromethane/methanol mixture in the presence of catalytic amounts of lithium

Scheme 3. Purification of **10**



(6) (a) Tietze, L. F.; Dölle, A.; Schiemann, K. *Angew. Chem., Int. Ed.* **1992**, *31*, 1372. (b) Tietze, L. F.; Schiemann, K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851. (c) Tietze, L. F.; Wegner, C.; Wulff, C. *Synlett* **1996**, 471. (d) Tietze, L. F.; Wegner, C.; Wulff, C. *Eur. J. Org. Chem.* **1998**, 1639. (e) Tietze, L. F.; Weigand, B.; Völkel, L.; Wulff, C.; Bittner, C. *Chem.—Eur. J.* **2001**, *7*, 161. (f) Tietze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M. *Chem. Eur. J.* **2001**, *7*, 1304. (g) Tietze, L. F.; Hölsken, S.; Adrio, J.; Kinzel, T.; Wegner, C. *Synthesis* **2004**, 2236.

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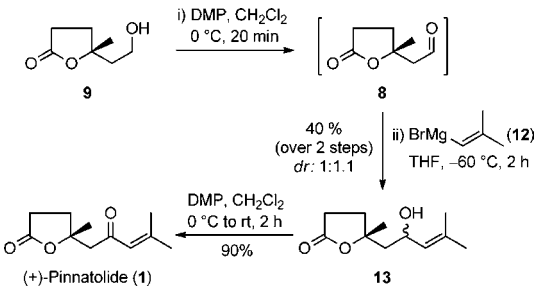
(9) (*R*)-**9** is a known compound and was obtained from the natural product nerol: (a) Ichihara, A.; Miki, S.; Kawagishi, H.; Sakamura, S. *Tetrahedron Lett.* **1989**, *30*, 4551. (b) Kayser, M. M.; Clouthier, C. M. *J. Org. Chem.* **2006**, *71*, 8424.

Scheme 4. Final Steps of the Total Synthesis



hydroxide at ambient temperature gave back the diastereopure alcohol (*R*,*R*)-**10** in quantitative yield.

It followed a hydrogenolysis using catalytic amounts of palladium on charcoal in THF/methanol at a hydrogen pressure of 1 atm and 45 °C to afford the γ-lactone alcohol (*R*)-**9** in quantitative yield and >99% *ee* (Scheme 2).

Mild oxidation of (*R*)-**9** with Dess-Martin periodinane (DMP)[11] in dichloromethane at 0 °C gave the labile γ-lactone aldehyde **8**, which was not further purified but directly treated with the commercially available dimethylvinyl Grignard reagent **12** in THF at −60 °C to afford the allylic alcohol (5*R*)-**13** in 40% yield over two steps as an approximately 1:1 mixture of epimers (Scheme 4). An elimination and readdition with the intermediary formation of an α, β-unsaturated aldehyde from **8** causing the loss of its stereointegrity were not observed.

Finally, DMP oxidation of the diastereomeric mixture (5*R*)-**13** in dichloromethane at ambient temperature led to (+)-(*R*)-Pinnatolide (**1**) in 90% yield. The enantiopurity was verified by analytical HPLC on chiral support to be >99%. Figure 2 shows the recorded CD and UV spectra of (+)-(*R*)-**1**.

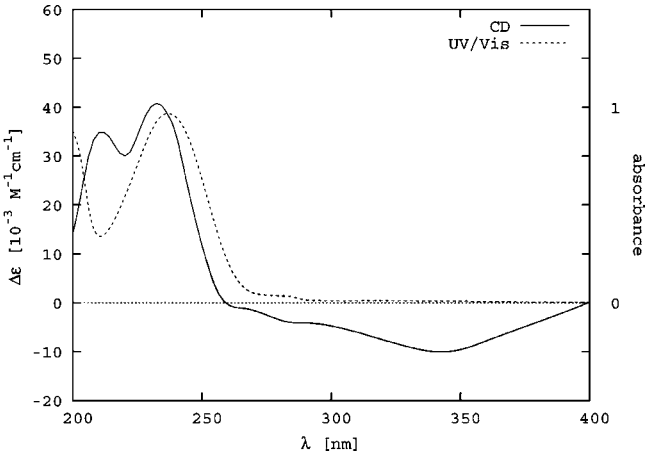


Figure 2. CD and UV spectrum of (+)-Pinnatolide (**1**).

In summary, we have developed an efficient synthesis of enantiopure (+)-(*R*)-Pinnatolide (**1**) using an asymmetric multicomponent domino allylation reaction as the key step.

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Supporting Information Available. Experimental procedures and full analytic data for all compounds as well as the crystallographic data of (*R*,*R*)-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(10) Figure and crystallographic data of dinitrobenzoate **11** are presented in the Supporting Information.

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