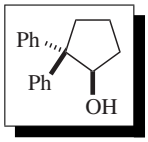
(*R*)-(–)-2,2-Diphenylcyclopentanol



[126421-67-8] $C_{17}H_{18}O$ (238.1358)

InChI = 1/C17H18O/c18-16-12-7-13-17(16,14-8-3-1-4-9-14)15-10-5-2-6-11-15/h1-6,8-11,16,18H,7,12-13H2/t16-/m1/s1

InChIKey = TYFASEURNPWTII-MRXNPFEDBQ

(chiral auxiliary in asymmetric synthesis)

Physical Data: a white solid,[1,2,3] mp 76–77 °C; $[\alpha]_D^{20}$ - 116 (*c* 0.97, EtOH).[1]

Solubility: soluble in most common organic solvents including acetone, DMSO, MeOH, EtOH, Et_2O, CH_2Cl_2, THF, and EtOAc.

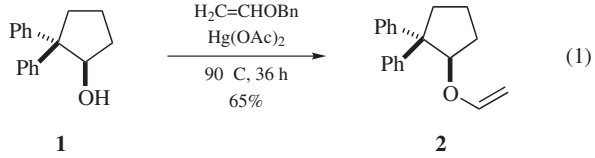
Analysis of Reagent Purity: by ^{1}H NMR and X-ray analyses[1] of its (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-MTPA] derivative;[2]chiral HPLC analysis; supercritical fluid chromatography (SFC).[4]

Preparative Methods: on a preparative scale (>97% ee) by borane reduction of 2,2-diphenylcyclopentanone in the presence of (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2] oxazaborole;[3,4] by asymmetric reduction of 2,2-diphenylcyclopentanone with (+)-β-chlorodiisopinocampheylborane;[1] by kinetic resolution of racemic acetate derived from the alcohol.[5]

Purity: recrystallization from hexane.[1,3,4]

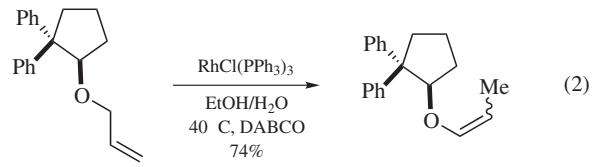
General. The potential of (*R*)-(–)-2,2-diphenylcyclopentanol (DCP) (**1**) as a chiral auxiliary was first demonstrated by d'Angelo,[1] who designed and employed the alcohol in a highly diastereoselective synthesis of β-amido esters. Later, Zhang et al.[6] were able to access diastereomerically enriched cycloalkanones via Mn(III)-based oxidative free-radical cyclizations of β-keto DCP esters. Denmark and co-workers have extensively studied the use of DCP as a chiral auxiliary on vinyl ether dienophiles employed in the Lewis-acid-promoted tandem [4 + 2]/dipolar [3 + 2] cycloadditions with nitroalkenes. DCP has expanded the utility of the tandem nitroalkene cycloadditions, especially in the application of *Z*-propenyl ethers and exo [4 + 2] cycloadditions. The effectiveness of this auxiliary is attributed to the alcohol containing a single asymmetric center (that bears a hydroxyl group) and a quaternary carbon center (bearing two phenyl groups) α to the hydroxyl group. Because one of the two geminal aromatic nuclei is necessarily gauche (synclinal) to the adjacent hydroxyl function, the appropriate special relationship exists for masking one of the π-faces in the corresponding dienophile.[1]

Synthesis of Vinyl Ethers of (*R*)-(–)-2,2-Diphenylcyclopentanol. The preparation of DCP-derived vinyl ethers usually involves mercuric acetate-catalyzed transetherification reaction with DCP and a corresponding vinyl ether (eq 1).[4]



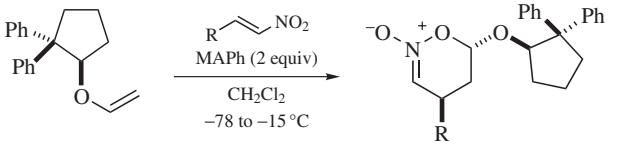
1 **2** (1)

E- and *Z*-Propenyl ethers (**4**) of DCP have been prepared by the isomerization of the corresponding allyl ethers in the presence of Wilkinson's catalyst and DABCO (eq 2).[4]

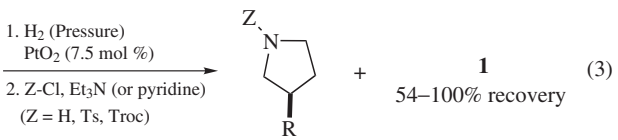


3 **4** 1.3:1 *Z*/*E* (2)

Synthesis of Substituted Pyrrolidines. A cycloaddition/reduction sequence between nitroalkenes and vinyl ethers derived from DCP, i.e., **2** can effect the enantioselective synthesis of substituted pyrrolidines.[7,8] 2-Substituted 1-nitroalkenes undergo highly efficient and diastereoselective Lewis-acid-promoted [4 + 2] cycloaddition with DCP-derived vinyl ethers to afford cyclic nitronates **5** in high yields. Subsequent reduction with PtO_2 (7.5 mol %), under 160 psi of H_2 at room temperature for 24 h, affords the optically active 3-substituted pyrrolidines (**6**) (71–97%, both as the free base and *N*-protected derivatives), and the chiral auxiliary **1**[8] (eq 3).



2 **5**

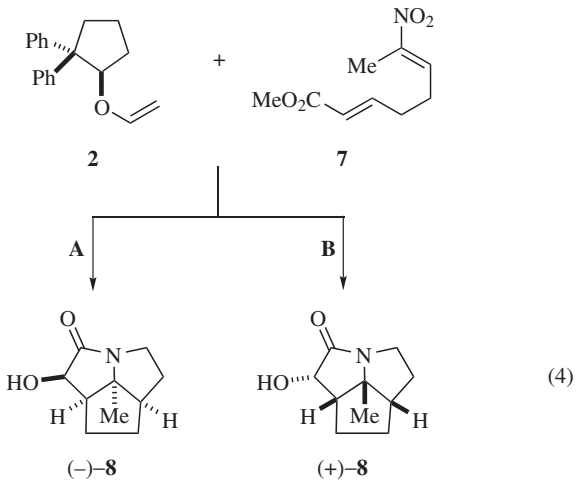


6
69–80% yield
71–97%ee

(3)

R = Ph, *t*-Bu, veratryl, *n*-pentyl, cyclohexyl, —$(CH_2)_4CO_2$-*t*-Bu

The choice of Lewis acid promoter for these reactions can change the sense of asymmetric induction.[4,8–12] For example, tandem [4 + 2]/ [3 + 2] cycloadditions (eq 4) mediated by Ti(O-*i*-Pr)$_2Cl_2$, followed by hydrogenolysis afforded tricyclic (–)-α-hydroxy lactam [(–)-**8**] in 98% ee. When mediated by methylaluminum-bis(2,6-diphenylphenoxide) (MAPh), the same reaction gave (+)-**8** in 93% ee. Importantly, the observed selectivity is not chiral auxiliary dependent.[4,8,9] Rather, it is attributed to a highly endo selective cycloaddition in the case of Ti compared to high exo selectivity in the case of MAPh.

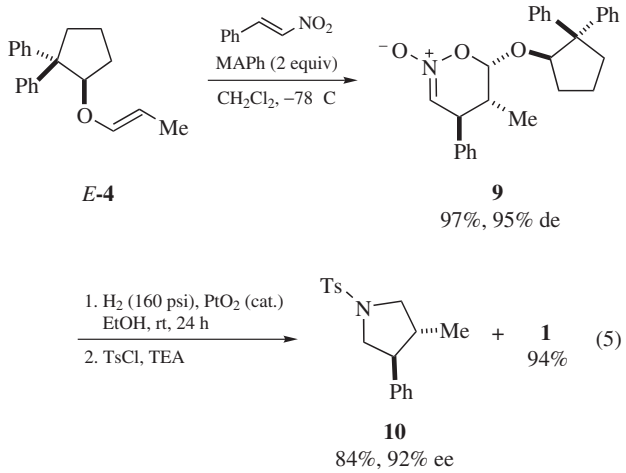


(4)

Conditions **A**: 1. $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, CH_2Cl_2, –78 °C (89%)
2. H_2, Raney Ni, MeOH (70%)

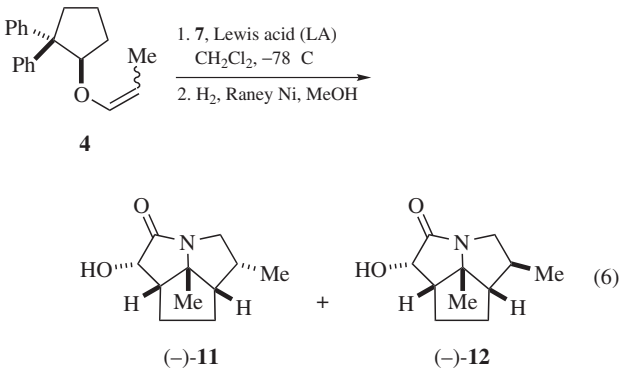
Conditions **B**: 1. MAPh, CH_2Cl_2, –78 °C (86%)
2. H_2, Raney Ni, MeOH (74%)

The use of DCP-derived propenyl ethers in nitroalkene [4 + 2] cycloaddition allows for the installation of an additional stereogenic center in the tandem cycloadducts. The methyl substituent also provides a stereochemical marker to allow for the determination of endo/exo selectivity in the [4 + 2] cycloaddition.[4] DCP-derived *E*-propenylvinylether (*E*-**4**) has been employed in the asymmetric synthesis of 3,4-disubstituted pyrrolidines.[8] MAPh-promoted [4 + 2]-cycloaddition of the vinyl ether with *trans*-β-nitrostyrene provided a 20:1 mixture of diastereomeric nitronates **9** in 97% yield (eq 5). Subsequent room-temperature hydrogenolysis (160 psi H_2) with catalytic PtO_2 in EtOH provided a 20:1 mixture of trans- and cis-methyl-3-phenylpyrrolidine. Following this reduction, *N*-protection afforded the diastereomerically pure trans-4-methyl-3-phenylpyrrolidine (**10**) in 84% yield and 92% ee[8] along with **1** (94% recovery following SiO_2 chromatography).



(5)

Synthesis of α-Hydroxy Lactams. Propenylethers of DCP have also been employed in the synthesis of α-hydroxy lactams.[4] The *Z*- and *E*-isomers show different levels of selectivity in the presence of MAPh or $Ti(O\text{-}i\text{-}Pr)_2Cl_2$(eq 6). When promoted by MAPh, the *Z*-propenyl ether undergoes exo selective [4 + 2] cycloadditions; in contrast, endo selective [4 + 2] cycloadditions are observed when the reactions are promoted by $Ti(O\text{-}i\text{-}Pr)_2Cl_2$.[4] MAPh-promoted cycloaddition of the *E*-propenyl ether afforded a single α-hydroxy lactam [(+)-**11**] derived from exclusive exo approach of the dienophile in the [4 + 2] cycloaddition.[4] Reactions of the *E*-propenylether is less selective with $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, affording exo and endo products in the ratio of 2.3:1.0. Although the exo diastereomer [(−)-**12**] was found to be highly enantiomerically enriched (96% ee), this erosion of endo/exo selectivity can be viewed as a shortcoming of DCP (**1**) as a chiral auxiliary.

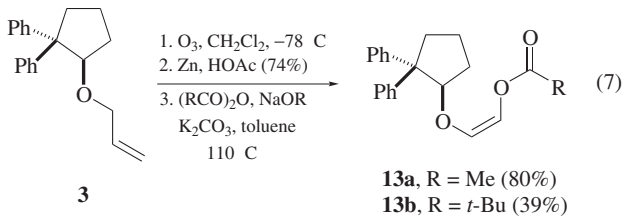


(6)

For *Z*-**4**:
w/ LA= $Ti(O\text{-}i\text{-}Pr)_2Cl_2$: (–)-**11** (92%ee)/(–)-**12** (65%ee) (endo:exo) ~8:1
w/ LA= MAPh: (–)-**11** (38%ee)/(+)-**12** (83%ee) (endo:exo) ~1:10.

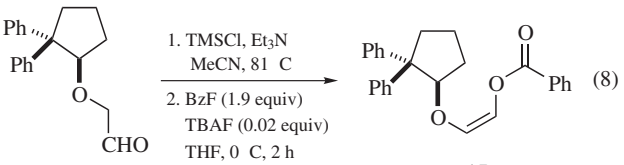
For *E*-**4**:
w/ LA= $Ti(O\text{-}i\text{-}Pr)_2Cl_2$: (–)-**11** (66%ee)/(–)-**12** (96%ee) (endo:exo) 1:2.3
w/ LA= MAPh: (+)-**11** (74%ee) (exclusive product).

Synthesis and Reaction of 2-(Acyloxy) and 2-(Benzoyloxy) vinyl Ethers of (*R*)-(–)-DCP. 2-(Acyloxy)vinyl ethers (**13**) of DCP[7] have been prepared (eq 7). Allylation of **1** followed by ozonolysis with a zinc/acetic acid reductive work-up affords the corresponding chiral aldehyde. Heating this aldehyde with the appropriate anhydride and sodium salt of the carboxylic acid gives the desired 2-(acyloxy)vinyl ethers.



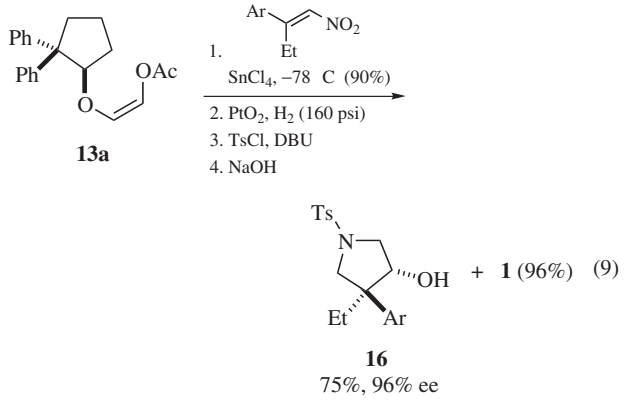
(7)

A more efficient route to 2-(benzoyloxy)vinyl ether (**15**)[13] involves (0 °C, THF) conversion of the chiral alkoxy aldehyde **14** to its silyl enol followed by *O*-acylation with benzoyl fluoride and a catalytic amount of TBAF (2 mol %) to form a separable mixture of the *Z*-vinyl ether (81%) and *E*-vinyl ethers (6%) (eq 8).



14 **15** (81% *Z* + 6% *E*) (8)

Compound **13a** exhibits high π-facial selectivity in the regioselective [4 + 2] cycloaddition (promoted by $SnCl_4$) with 2,2-disubstituted aryl-1-nitroalkenes affording *N*-tosyl-4,4-disubstituted-3-hydroxypyrrolidines (**16**) in high enantiomeric excess (96%) (eq 9).[7]

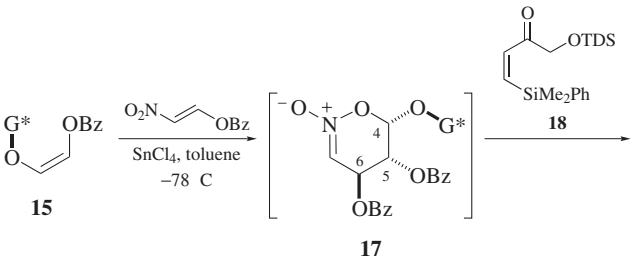


13a **16** 75%, 96% ee (9)

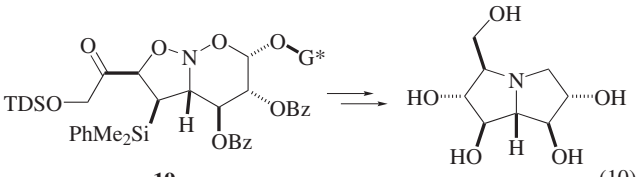
DCP-based Chiral Auxiliaries in Total Synthesis. DCP-based chiral auxiliaries have proven amenable to asymmetric total synthesis, including Denmark's syntheses of of the pyrrolizidine alkaloid (–)-rosmarinecine[10] and the pentahydroxy pyrrolizidine alkaloid (+)-casuarine.[13,14] Denmark's synthesis of (+)-casuarine involves [4 + 2] cycloaddition of dienophile **15** with nitrobenzoate followed by [3 + 2] cycloaddition of the resulting nitronate **17** with a vinyl silane **18** (eq 10). During formation of the [4 + 2] cycloadduct, the relative configuration between C4 and C5 is a direct consequence of the vinyl ether geometry, while the stereochemistry at C6 is determined by the ability of the chiral auxiliary to differentiate the diastereotopic π faces (*Re* of Si) of the vinyl ether (termed internal diastereoselection). Thus, this tandem sequence establishes five of the six stereocenters present in the natural product. Moreover, the chiral auxiliary **1** is recovered in 99% yield after hydrogenolysis (260 psi H_2) with Raney nickel in MeOH followed by SiO_2 chromatography.

Synthesis of Chiral β-Amido Esters. The use of **1** as a chiral auxiliary in the asymmetric hydrogenation (H_2/PtO_2) of stereogenic β-acetamidocrotonates has also been reported.[1] Reaction of **1** with diketene in the presence of TEA and acetone as solvent, followed by saturation with NH_3, then Ac_2O-pyridine, and finally hydrogenation (PtO_2, 3–5 bars of H_2) afforded the β-amido esters (**22**) in high selectivity (96% de) (eq 11).

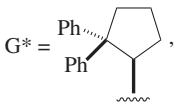
DCP as a Chiral Controller in Oxidative Free Radical Cyclizations. As a chiral auxiliary, DCP (**1**) is also reported to induce modest diastereoselection (60% de) in Mn(III)-based oxidative free-radical cyclizations[6] of β-keto esters (eq 12). Chiral β-keto ester **25** was prepared by transesterification reaction with methyl ester **23**, **1**, and 0.3 equiv of DMAP (catalyst) in anhydrous toluene at reflux for 3–5 d as described by Taber.[15] Oxidative cyclization of a 0.1 M solution of **24** in AcOH with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_3 \cdot H_2O$[6] provided bicyclo[3.2.1]octan-2-one (**25**).



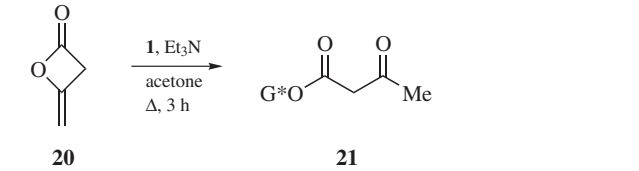
15 **17**



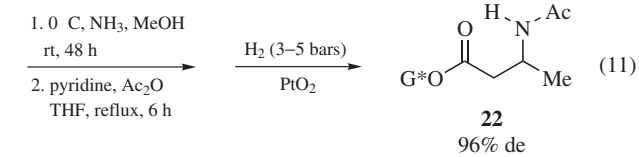
19 (+)-Casuarine (10)



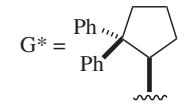
TDS = thexyl dimethylsilyl

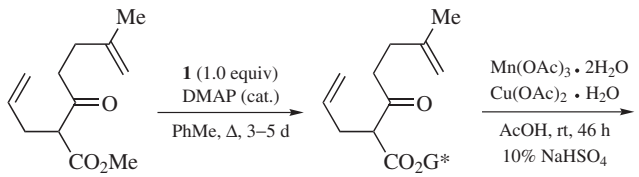


20 **21**



22 96% de (11)

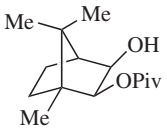




23 **24**

25 (12)

Related Reagents. Though not always as efficient as DCP (**1**), camphor derivatives (**26**),[4,7,11] (–)-8-phenylmenthol (8-PhM) (**27**);[1,5,6,10] (1*R*,2*S*)-2-phenylcyclohexanol (**28**);[1,4,5,7–9] and *trans*-2-(1-methyl-1-phenylethyl)cyclohexanol (**29**)[10] can also serve as chiral auxiliaries in asymmetric cycloadditions of vinyl and propenyl ethers with nitroalkenes (Figure 1). (*S*)-**1** can also be used, however, this enantiomer is relatively expensive to prepare by asymmetric borane reduction.



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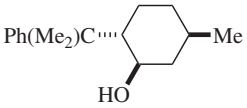

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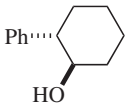

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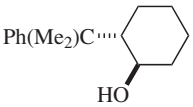

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