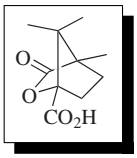
(–)-(1*S*,4*R*)-Camphanic Acid[1]



(1*S*)
[13429-83-9] $C_{10}H_{14}O_4$ (MW 198.22)
InChI = 1/C10H14O4/c1-8(2)9(3)4-5-10(8,6(11)12)14-7(9)13/h4-5H2,1-3H3,(H,11,12)/t9-,10+/m0/s1/f/h11H
InChIKey = KPWKPGFLZGMMFX-OFRSAFNYDV
(1*R*)
[67111-66-4]
InChI = 1/C10H14O4/c1-8(2)9(3)4-5-10(8,6(11)12)14-7(9)13/h4-5H2,1-3H3,(H,11,12)/t9-,10+/m1/s1/f/h11H
InChIKey = KPWKPGFLZGMMFX-PEBQTMIIDI
(±)
[465-48-5]
InChI = 1/C10H14O4/c1-8(2)9(3)4-5-10(8,6(11)12)14-7(9)13/h4-5H2,1-3H3,(H,11,12)/f/h11H
InChIKey = KPWKPGFLZGMMFX-WXRBYKJCCO

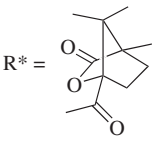
(enantiomeric purity determination;[2] chemical resolution;[3] chiral auxiliaries[4])

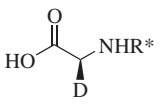
Physical Data: mp 201–204 °C; (1*S*): $[\alpha]_D$ −20.4° (*c* 1.71, dioxane); $[\alpha]_D$ −18° (*c* 1, dioxane).
Solubility: sol EtOH, ether, boiling H_2O, and AcOH.
Form Supplied in: white solid.
Preparative Methods: commercially available. Alternatively, the acid can be prepared in two steps from camphoric acid (1. PCl_5; 2. H_2SO_4; 65% overall yield). The acid can be converted to the corresponding acid chloride upon treatment with ***Thionyl Chloride*** (99% yield).[1,5]
Purification: crystallized from hot toluene.
Handling, Storage, and Precautions: stable; no special precautions.

Original Commentary

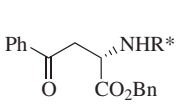
André B. Charette
Université de Montréal, Québec, Canada

Analysis of the Enantiomeric Purity of Alcohols and Amines. It has been shown that camphanic acid is an efficient chiral derivatizing agent for the determination of the enantiomeric purity of alcohols and amines.[2] A typical procedure involves mixing a solution of the amine or the alcohol (in CH_2Cl_2, py, or benzene) with camphanoyl chloride in the presence of a base (Et_3N, py, DMAP, or $NaHCO_3$). Alternatively, the substrate can be coupled directly with camphanic acid in the presence of DCC/DMAP. These conditions, however, can potentially lead to significant kinetic resolution.[6] Camphanic acid was initially developed for the analysis of the enantiomeric purity of α-deuterated primary alcohols[7] and amines.[8] Distinct signals by ^1H NMR for the two diastereomers can usually be observed upon addition of a chiral shift reagent or when using C_6D_6 as the solvent.[9] Since then, this chiral derivatizing agent has been widely used for measuring the enantiomeric excess of several classes of compounds such as α-monodeuterated glycine derivatives (**1**),[10] α- and β-amino acids (**2**, **3**),[11,12] α,α-disubstituted α-amino acids (**4**),[13] secondary alcohols (**5**),[14] 1,2-amino alcohols (**6**),[15] and sulfoximines.[16]

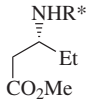




(1)



(2)



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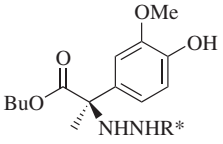
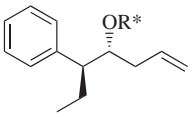
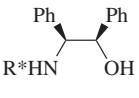


(4)

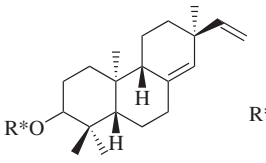


(5)

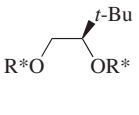


(6)

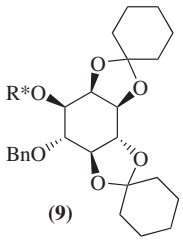
Resolution of Alcohols. In addition to generally providing highly crystalline derivatives that are usually suitable for X-ray crystallographic studies,[17] diastereomeric esters derived from camphanic acid have been widely used in organic synthesis for the resolution of racemic alcohols by fractional crystallization or chromatography.[18] This is one of the methods of choice to resolve inositol derivatives.[19] Selected examples are shown in (**7**)–(**10**).[20]



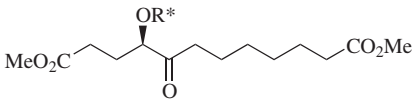
(7)



(8)

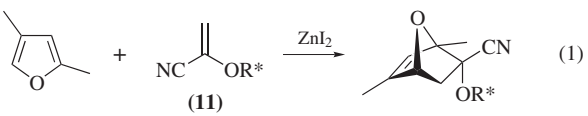


(9)



(10)

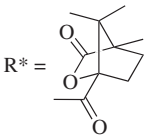
Chiral Auxiliary for Cycloaddition Reactions. Camphanate ester (**11**) has been used as a chiral dienophile in cycloaddition reactions with substituted furans to produce 7-oxabicyclo[2.2.1]-heptene derivatives (eq 1).[4,21]



(11)

54%
(after 2 recrystallizations)

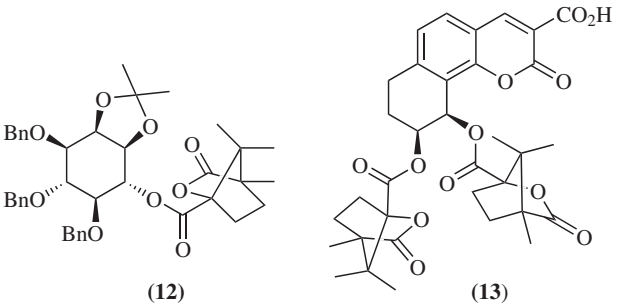
(1)



First Update

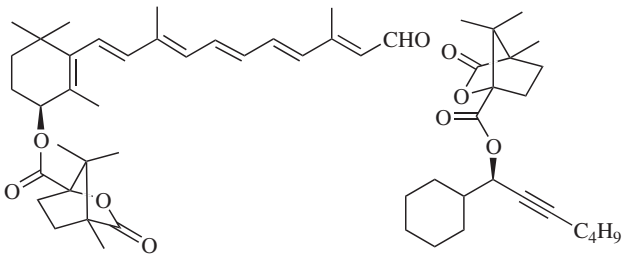
Qingwei Yao
Northern Illinois University, DeKalb, IL, USA

Reagent for the Determination of Enantiomeric Excess of Chiral Alcohols. Camphanic acid continues to find application as a useful derivatizing agent for the determination of the enantiomeric purity of chiral alcohols. This includes camphanate esters **12**–**15** formed from a *myo*-inositol derivative,[22] a cyclic diol,[23] (11*E*)-4-hydroxyretinal,[24] and a secondary propargyl alcohol,[25] respectively. The diastereomeric purity of the camphanate esters was analyzed by ^{1}H NMR (for **12** and **13**) or HPLC (for **15**).



(**12**)

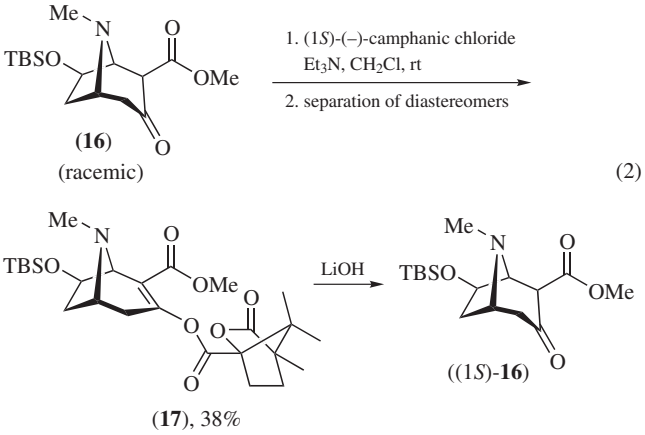
(**13**)



(**14**)

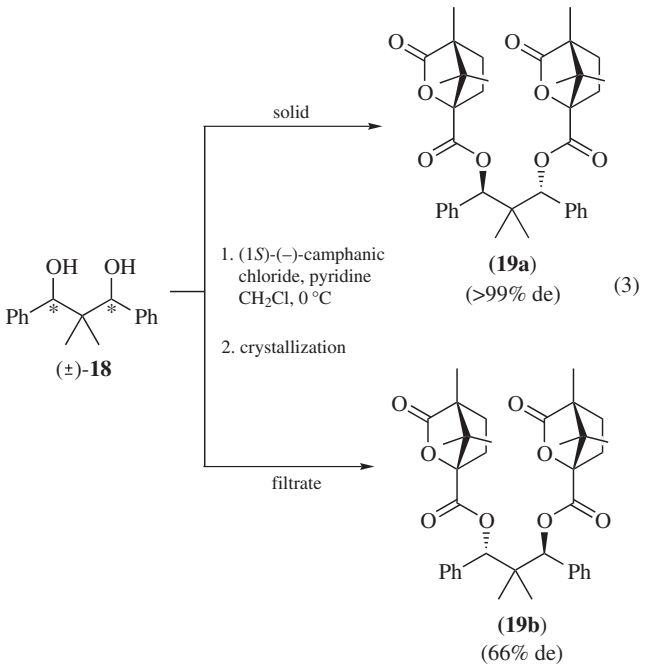
(**15**)

Resolution and Determination of Absolute Configuration of Alcohols and Related Compounds. Racemic ketoester **16** was derivatized to diastereomers of the enol camphanate ester with (1*S*)-camphanic chloride in the presence of triethylamine (eq 2).[26] Separation by column chromatography gave pure **17** whose stereochemistry was confirmed by single-crystal X-ray analysis. Subsequent cleavage of the enol ester of **17** with LiOH afforded (1*S*)-**16** in quantitative yield.



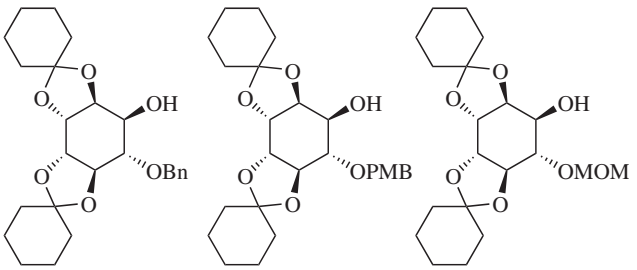
(2)

The resolution of (±)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol **18**, a C_2-symmetric and conformationally rigid acyclic diol, was achieved using (*S*)-camphanoyl chloride (eq 3).[27] The diesters **19a** and **19b** could be easily separated by crystallization from toluene. Saponification gave (*S*,*S*)-(+)-**18** and (*R*,*R*)-(–)-**18** in 99 and 66% ee, respectively. Attempted resolution through the separation of diastereomeric ester derivatives of (–)-menthylacetic acid, (+)-hydratropic acid, (–)-5-oxo-2-tetrahydrofurancarboxylic acid, and ketals of (+)-camphor all proved to be unsuccessful.



(3)

Using the procedures developed by Vacca et al. for the resolution of **9**,[20c] the *myo*-inositol derivatives **20**–**22**, were all resolved as their (1*S*)-camphanates.[28] The diastereomeric esters were separated chromatographically and the resolved alcohols were recovered after saponification with LiOH.



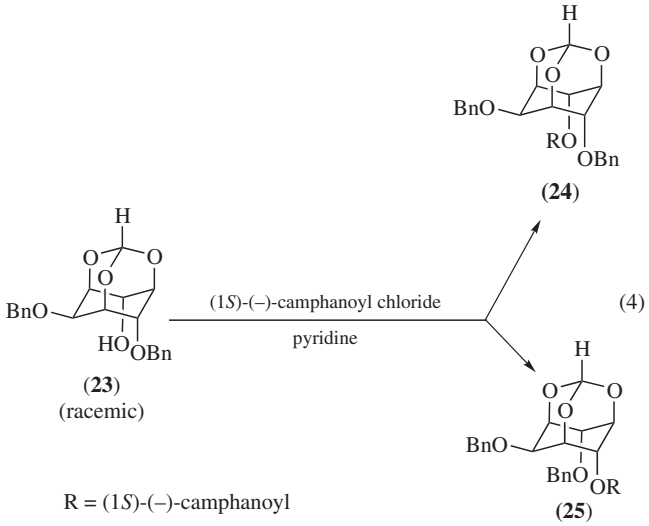
(**20**)

(**21**)

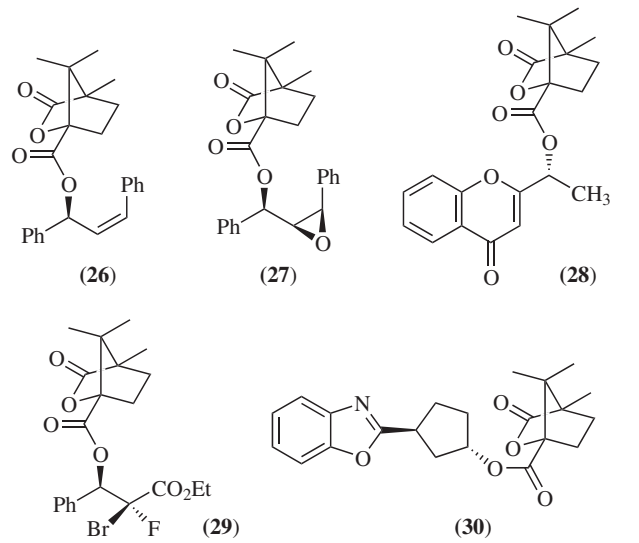
(**22**)

(1*S*)-(–)-Camphanoyl chloride was also used in a key resolution step for the synthesis of the enantiomers of 2,4-di-*O*-benzyl-*myo*-inositol, which are precursors for the synthesis of D- and L-*myo*-inositol 1,3,4,5-tetrakisphosphate. The racemic *myo*-inositol orthoformate **23** was converted to the diastereomeric camphanate esters **24** and **25** by acylation with (1*S*)-(–)-camphanoyl chloride.[29] Chromatographical separation of **24** and **25** followed by methanolysis with NaOMe in MeOH gave the two pure enantiomers of **23** which, after cleavage with TFA, led to the isolation of the two enantiomers of 2,4-di-*O*-benzyl-*myo*-inositol (eq 4). Attempted resolution of **23** with (1*S*)-(+)-10-camphorsul-

fonyl chloride proved unsuccessful because the diastereomeric camphorsulfonates could not be separated chromatographically.

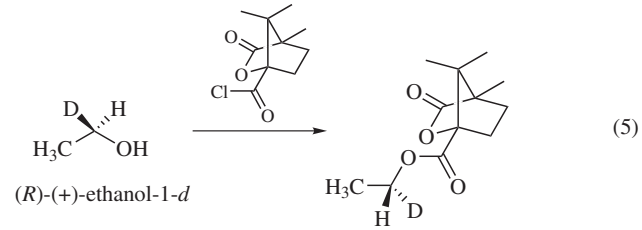


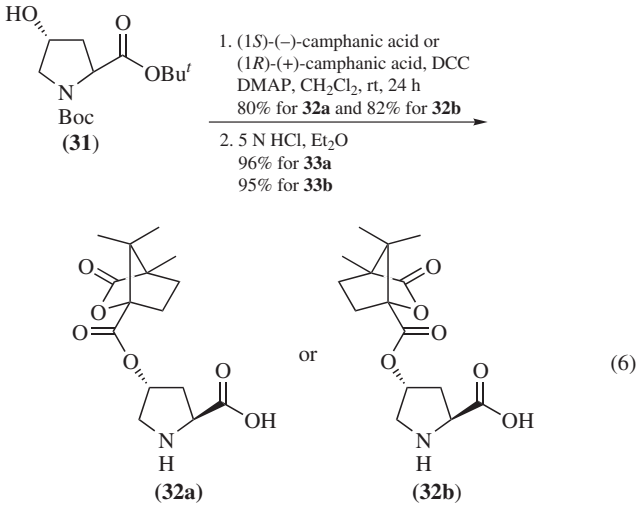
Among the chiral derivatization reagents, camphanic acid proves to be particularly suitable for the structural determination of secondary alcohols, since secondary camphanate esters are prone to crystallization. Selected examples of X-ray determination of absolute configuration of alcohols in the form of their camphanates are given below.[30]



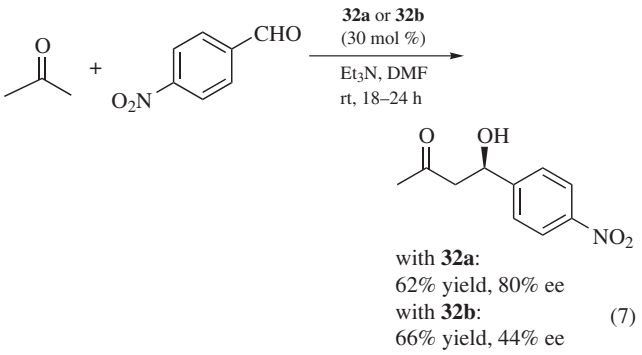
Determination of the Absolute Configuration of Chiral Ethanol-1-*d* by Neutron Diffraction. The absolute configuration of (+)-ethanol-1-*d*, prepared from the equilibration of CH_3CH_2OH in excess D_2O with yeast alcohol dehydrogenase (YADH), diaphorase, and nicotinamide adenine dinucleotide (NAD), has been determined to be *R* by single-crystal neutron diffraction analysis of its (−)-camphanate ester (eq 5).[31]

Chiral Modifier of 4-Hydroxylproline as Organocatalyst for Aldol Reactions. Modification of the hydroxyl group of 4-OH-proline **31** with camphanic acid led to the discovery of new organocatalysts **32a** and **32b** (eq 6).[32]





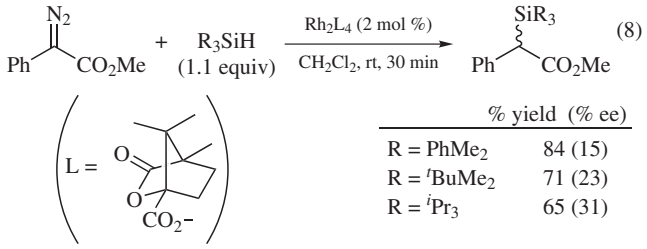
When used in the aldol reaction of acetone with *p*-nitrobenzaldehyde (eq 7), the (1*S*)-(−)-camphanic acid derivative **32a** led to improved enantioselectivity in aldol reactions compared to use of the unmodified L-4-hydroxyproline (80% vs. 70% ee). Interestingly, the (1*R*)-(+)-camphanic acid derivative **32b** gave much lower enantioselectivity.

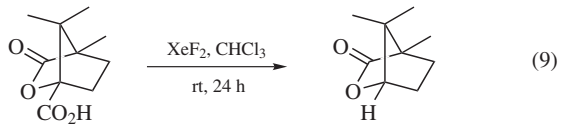


As Chiral Ligand for Rh(II)-catalyzed Asymmetric Carbene Insertion into the Si–H Bond. Decomposition of methyl 2-diazophenylacetate in the presence of a silane and a chiral dirhodium(II) catalyst results in Si–H insertion of the intermediate carbenoid. When a Rh(II) catalyst derived from (1*S*)-camphanic acid was employed, a moderate ee (15–31%) was obtained, with the bulkier silane $^{i}Pr_3SiH$ giving a better enantioselectivity albeit at the cost of a slight drop in the yield of the insertion product (eq 8).[33]

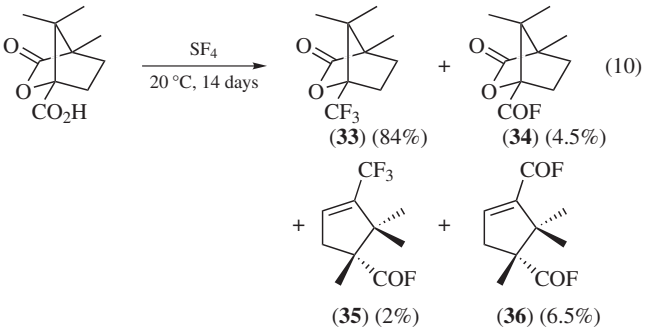
Miscellaneous Reactions and Applications. Camphanic acid underwent decarboxylation upon reacting with XeF_2 in chloroform through a free radical mechanism. Unlike primary carboxylic

acids, which yield alkyl fluorides when treated with XeF_2, camphanic acid afforded the corresponding alkane, pointing to hydrogen atom abstraction from the solvent (eq 9).[34]

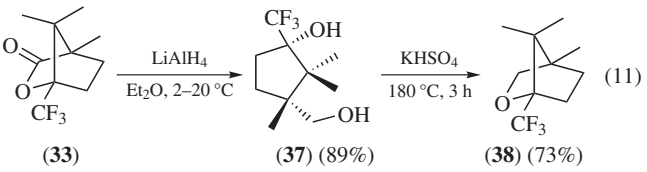




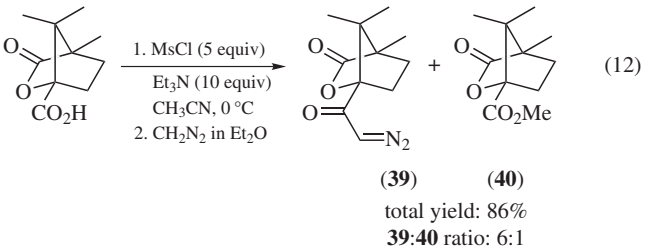
Fluorination of (1*S*)-(−)-camphanic acid with sulfur tetrafluoride afforded a mixture of several fluorinated optically active compounds (**33**–**36**) (eq 10).



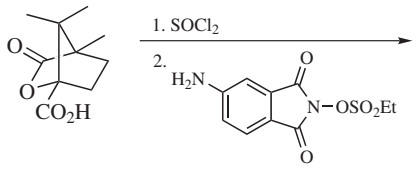
The major product **33** was isolated in 48% yield and further converted to fluorinated diol **37** and (1*R*,4*S*)-(−)-3-oxa-4-(trifluoromethyl) bornane **38** (eq 11).[35]

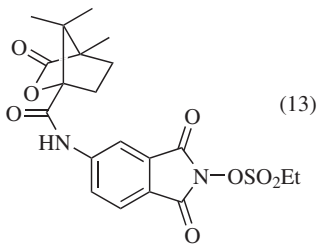


Camphanic acid was used as the precursor for the synthesis of diazoketone **39** (eq 12). The use of CH_3CN as solvent in this reaction was the key to obtaining a high yield of the diazoketone, as less polar solvents such as toluene and THF tended to increase the formation of the methyl ester by-product **40**.[36]



A camphanamide **42** derived from the amine **41** containing a 1*H*-isoindole-1,3-dione moiety was synthesized from (1*S*)-(−)-camphanic acid and shown to be a potent inhibitor of human leukocyte elastase (HLE) with a $k_{obs}/[I]$ = 11 000 M^{-1} s^{-1} (eq 13).[37] Interestingly, the antipode derived from (1*R*)-(+)-camphanic acid is a much less potent inhibitor of HLE.





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