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Synthesis, Stereostructure, and Conformations of Novel Bi- and Trifunctional (+)-Isomenthone Derivatives

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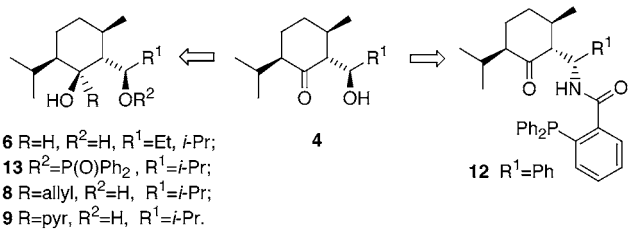
ABSTRACT



6 R=H, R^2=H, R^1=Et, *i*-Pr;
13 R^2=P(O)Ph_2, R^1=*i*-Pr;
8 R=allyl, R^2=H, R^1=*i*-Pr;
9 R=pyr, R^2=H, R^1=*i*-Pr.

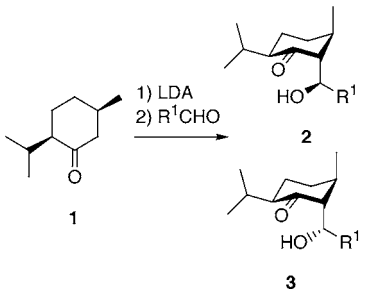
4

12 R^1=Ph

Following protection, keto alcohols 4 [from (+)-isomenthone] undergo reduction to 1,3-diol 6 (*S* configuration at the new stereocenter). Organometallic *C*-nucleophiles add to the carbonyl with the same facial selectivity as hydride, providing multifunctional derivatives, e.g., 8 and 9, with five contiguous stereocenters. The side chain hydroxyl of 4 is elaborated into amino and amide derivatives (e.g., 12). Structural analysis shows that 6, 8, 9, and the precursor to 12 (10) all adopt triaxial solid-state conformations.

A considerable number of terpenoid derivatives are useful chiral controllers in asymmetric synthesis,[1] including some very effective chiral reagents (e.g., allylboron reagents), chiral auxiliaries (e.g., 8-phenylmenthol), and chiral catalysts. While menthone has provided the chiral information in many systems, applications of isomenthone derivatives are essentially unknown. Carbon−carbon bond formation to the kinetic enolate of menthone (at C6) is generally not diastereospecific, and most elaborations from menthone have thus been at the carbonyl group. We have previously shown that aldol reactions of (+)-isomenthone (**1**) with a wide range of aldehydes are all completely diastereospecific in C−C formation to C6 with the same sense of diastereocontrol at the new C6 center (to **2** and/or **3**) (Scheme 1).[2] This offers the potential of elaborating isomenthone into bi- and trifunctional ligands by elaboration at both the terpene carbonyl and at the α methylene, without complications from generating mixtures of ring diastereomers.

Scheme 1



1 **2** **3**

While the new C6 stereocenter is introduced with complete control, *Re* or *Si* selectivity for addition to the carbonyl group

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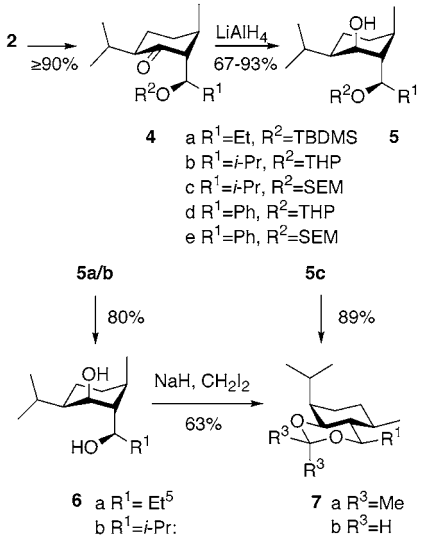
of either alkyl or aryl aldehydes is in most cases not specific, providing threo/erythro mixtures, though in some cases, a single (threo) diastereomer is obtained. The diastereoselectivity can be affected by modifying conditions; separation of diastereomers, if desired, is achievable through chromatography or crystallization.[2]

While (+)-isomenthone itself has been shown to exist in solution mainly as the diastereomer with isopropyl group axial,[3] all aldol derivatives we have prepared adopt the conformation shown in Scheme 1 (at least in the solid state) with the isopropyl equatorial and the hydroxylated side chain disposed axial (even when this hydroxylated group is aromatic or branched).[2] Recently, an extensive study of solid state and solution conformations and aggregation states of cycloalkanone-derived aldols (without α,α′-disubstitution) has appeared.[4] We will describe more extensive structural analyses (by X-ray crystallography and NMR) of isomenthone-derived aldols elsewhere.[2b]

We have sought to utilize this homologation to provide a versatile entry to new derivatives, which, through elaboration of the ring carbonyl and/or side chain hydroxyl, could provide novel bi- and trifunctional systems containing five contiguous chiral centers. We report here the conversion of (+)-isomenthone to examples of novel diols, of amino alcohols and derivatives, and of thioalcohols. This establishes the viability of using isomenthone as a starting material for diverse new ligand candidate synthesis via ring diastereospecific aldol homologation intermediates.

We previously established that reduction of the keto alcohol **2** (R^1 = Et) and its silyl ether derivative **4a** introduced the new secondary alcohol center with *S* configuration with high selectivity.[5] To assess whether other keto alcohols **2** and derivatives were reduced with comparable diastereocontrol, both THP ether derivative **4b**, and SEM ether derivative **4c**, of the isopropyl system **2** (R^1 = isopropyl) were prepared and reduced using LAH. This afforded almost exclusively one configuration at the new chiral center giving (after deprotections) **6a**/**b** from **5a**/**b** (Scheme 2).[5] Reaction of diol **6** with diiodomethane gave the (conformationally locked) methylene acetal product **7b**. Attempted removal of the SEM ether of **5c** with TFA did not provide diol (**6b**), but instead directly afforded the same methylene acetal **7b**. This proved that reduction of both SEM- and THP-protected systems (**4**) proceed with the same sense of diastereocontrol. Similarly, **6a** forms isopropylidene acetal **7a**, facilitating NMR proof of absolute stereochemistry of reduction in the case of **6a**.

Scheme 2



The stereostructure of **6b** obtained from reduction of **4b** with LAH (then THP removal) was established directly through X-ray structure analysis (Figure 1). This then allowed assignment of the structure of acetal **7b** as the *trans*-decalin system shown. These results indicate that reduction of unprotected or SEM-, TBDMS-, or THP-protected aldols, with either of two different hydride sources[5] and applied to two different aldol substrates, proceeds with a common sense of diastereoselectivity in creation of the new alcohol-bearing stereocenter in all cases. It is likely that reductions of other related keto alcohol derivatives would proceed with good diastereocontrol in this same sense.

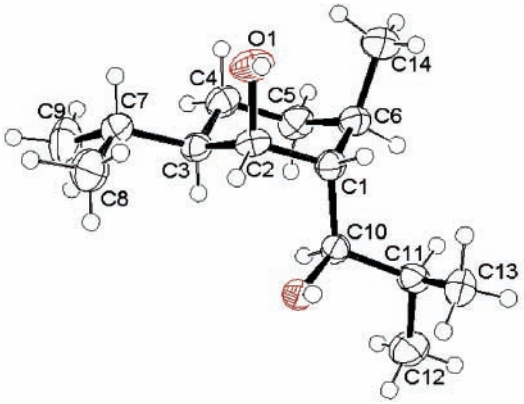


Figure 1. X-ray structure of **6b**.

The X-ray structure shows that diol **6** adopts the conformer shown placing three ring substituents axial, with only the ring isopropyl group equatorial. Crystal forces may be

(1) (a) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935−952. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: New York, 2000. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999.

(2) (a) Chughtai, J. H.; Gardiner, J. M.; Harris, S. G.; Parsons, S.; Rankin, D. W. H.; Schwalbe, C. H. *Tetrahedron Lett.* **1997**, *38*, 9043−9046. (b) Gardiner, J. M.; Chughtai, J. H.; Crewe, P. D.; Smith. G. E.; Veal, K. T.; Warrren, J. E.; Pritchard, R. G.; Harris, S. G.; Parsons, S.; Rankin, D. W. H.; Schwalbe, C. H. Unpublished work.

(3) Smith, W. B.; Amezcua, C. *Magn. Reson. Chem.* **1998**, *36*, S3−S10.

(4) Kitamura, M.; Nakano, K.; Miki, T.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* **2001**, *123*, 8939−8950.

(5) Gardiner, J. M.; Chughtai, J. H.; Sadler, I. H. *Tetrahedron*: *Asymmetry* **1998**, *9*, 599−606. Both $NaBH_4$ and $LiAlH_4$ gave the same sense of diasterecontrol.

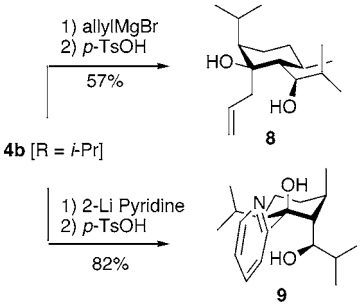
responsible for this triaxial conformational preference in the solid state, since the diol forms asymmetric dimers held together by H-bonding between the two oxygens of one molecule and the two hydroxyl protons of the other molecule. However, ^{1}H NMR of both **6** and its diacetate show that the proton on the ring hydroxyl-bearing carbon (C2) does not have any diaxial coupling. Thus, the same conformation with three groups disposed axially is adopted both in solution and in the solid state.

With reduction routes available to convert different keto alcohols to chiral 1,3-diols and monoprotected derivatives whose absolute structures are now defined, this chemistry should allow ready provision of further diol analogues as well as to 1,3-diol derivatives (e.g., phosphinites) as novel chiral ligand candidates. We have adapted this chemistry to the synthesis of diol libraries of this type showing that a range of funtionalized aldols can be prepared, reduced, and screened as ligands in parallel to identify new enantioselective chiral ligands.[6] There is one related example of a menthone-derived 1,3-diol of this sort, an aluminum complex of which catalyzes a Diels−Alder reaction with up to 82% ee.[7]

Our second target was the addition of nonhydride nucleophiles to the ring carbonyl to introduce a new C−C bond and adding new functionality along with a new hydroxylated quaternary center.

Two illustrative examples are presented here of reactions of protected aldol **4b** with Grignard and organolithium reagent. Allylmagnesium bromide reacts with **4b** to give a single diastereomeric product **8**, while 2-lithiopyridine reacted with **4b** also giving, after deprotection, a single diastereomeric product **9** (Scheme 3). In both cases, the

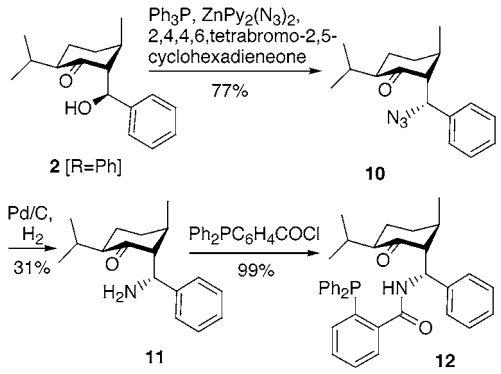
Scheme 3



nucleophile has added with the same facial sense as with hydride additions. This strongly suggests a general preference for any additions to this carbonyl of this substrate type. This predictivity is valuable for synthesis of further defined diastereomeric targets from various aldol intermediates. The pyridyl system **9** has an interesting trifunctional ligand architecture. The most related prior example is a menthyl-derived system without the side chain attached.[8] This illustrates that this chemistry provides a route into new families of more functionalized chiral ligand candidates.

We also wished to differentiate the two functional groups of the keto alcohols to demonstrate entry to various other new *bifunctional* and also *trifunctional* ligand types. Our route for introduction of nitrogen was via preparation of the azide derivative of (+)-isomenthone-derived aldol products. Attempts to introduce the azido group into **4b**, **4c**, or **2**/**3** (R^1 = Ph) through mesylation, tosylation, or triflation were unsuccessful due to competing side reactions. The azide was successfully introduced through a Mitsunobu-type reaction, using 2,4,4,6-tetrabromo-2,5-cyclohexadienone, triphenylphosphine, and the diazobis(pyridine) zinc.[9] Thus, keto alcohol **2** [R^1 = Ph] was converted into azido ketone **10** in good yield (Scheme 4). Replacement of OH by the azido group excludes

Scheme 4



effects of H-bonding by the hydroxyl in driving conformational preference in the crystal structure (for the axial side chain). However, an X-ray structure of azide **10** shows the same ring conformation as in all keto alcohols, so that H-bonding from the aldol hydroxyl does not appear to be determining in conformational preferences in the solid state for (+)-isomenthone derivatives. The same azidation chemistry was successfully applied to **3** [R^1 = CH=CHPh].

This entry to 1,3-azidoketones provides a valuable hub, since both the azide and carbonyl groups could be elaborated to other functionality. There are recent examples of terpenoid-derived amino alcohols acting as effective catalysts.[10] In this context, we reduced the azide to an amino ketone by hydrogenation (unoptimized) to provide **11**, and this was then further elaborated to the amido phosphine **12** (Scheme 4). The combination of P, N, O functionality, frequently including an amide, is heterofunctionality common to several recently reported chiral ligands catalyzing various processes.[11]

(6) Gardiner, J. M.; Crewe, P. D.; Smith, G. E.; Veal, K. T. Unpublished results, 2002. Ligands identified with up to 90% ee.

(7) Naraku, G.; Hori, K.; Ito, Y. N.; Katsuki., T. *Tetrahedron Lett.* **1997**, *38*, 8231−8232.

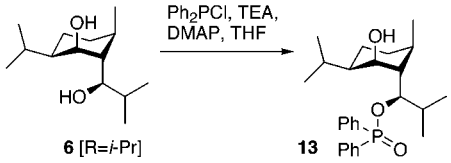
(8) Herrmann, W. A.; Haider, J. J.; Fridgen, J.; Lobmaier, G. M.; Spiegler, M. *J. Organomet. Chem.* **2000**, *603*, 69−79.

(9) (a) Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, *38*, 3955. (b) Viaud, M. C.; Rollin, P. *Synthesis*, **1990**, 130.

(10) (a) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809. (b) Panev, S.; Linden, A.; Dimitrov, V. *Tetrahedron: Asymmetry* **2001**, *12*, 1313−1321. (c) Dimitrov, V.; Dobrikov, G.; Genov, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1323−1329.

We also sought to convert diols of type **6** into bisphosphines (by double substitution of bistriflates or tosylates) or bisphosphinites from the diol by phosphinylation. Attempts at generating bisphosphines were unsuccessful. However, reaction of diol **6** [R^1 = *i*-Pr] with bisphenylphosphoryl chloride led to formation of (oxidized) monophosphorylated **13** (Scheme 5).

Scheme 5

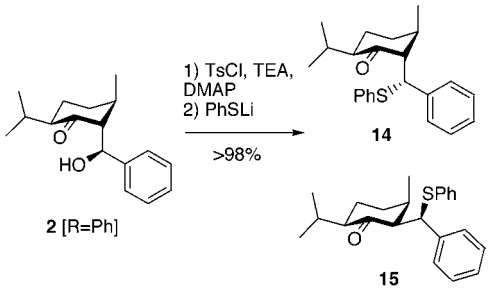


6 [R=*i*-Pr] **13**

To introduce a thiol function, the tosylate derivative of keto alcohol **2** [R^1 = Ph] was reacted with lithium thiophenoxide. Two thioether products **14** and **15** were formed, the minor (**15**) being that from concomitant substitution and C6 epimerization (Scheme 6). This is the only example where we have ever seen any epimerization chemistry and may be accounted for by the basicity of lithium thiophenoxide.

In conclusion, this work has shown that diastereospecific aldol elaborations of (+)-isomenthone allows entry to an array of different ligand architectures and functionalities containing two or three heteroatoms. This chemistry can now be exploited to construct ranges of new bi- and trifunctional ligands for evaluation in other target systems.

Scheme 6



2 [R=Ph]

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Supporting Information Available: ^{1}H, ^{13}C/DEPT, COSY, and HMBC spectra are available for compounds **6**, **8**, **9**−**11**, **13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Mino, T.; Kashihara, K.; Yamashita, M. *Tetrahedron*: *Asymmetry* **2001**, *12*, 287−291. (b) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, 65, 7033. (c) Uozumi, Y.; Mizutani, K.; Nagai, S.-I. *Tetrahedron Lett.* **2001**, *42*, 407. (d) Uozumi, Y.; Yasoshima, K.; Miyachi, T.; Nagai, S.-I. *Tetrahedron Lett.* **2001**, *42*, 411. (e) Hou, D. R.; Burgess, K. *Org. Lett.* **1999**, *1*, 1745−1747. (f) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237−2240.