# Highly Diastereoselective Aldol Reactions with Camphor-Based Acetate Enolate Equivalents

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New lithium enolates of α-hydroxy ketones, derived from camphor, are evaluated for asymmetric aldol reactions in the presence of lithium chloride. The diastereoselectivity of the reactions between the lithium enolate of **3** and a variety of achiral aldehydes is strongly influenced by the lithium chloride salt. In these instances, the achieved levels of asymmetric induction, typically 95:5 dr, are in the range of those attained in aldol reactions involving the lithium enolate of the methyl ketone **4**, which is sterically more demanding. The resulting aldol adducts are easily transformed into *β*-hydroxy carboxylic acids, ketones, and aldehydes with concomitant recovery of the camphor, the chiral controller of the process, which can be reused.

## Introduction

The asymmetric aldol reaction has become a major tool for the stereocontrolled construction of carbon−carbon bonds.[1] The significance of this reaction stems from the fact that the aldol or derived 1,3-dioxygenated functionality is a key structural element of important classes of natural products or their precursors, including macrolides, ionophores, and *β*-lactam antibiotics.[2] Among the methodologies developed in the asymmetric aldol reaction,[1,3] the version that uses carboxylic acid derived chiral enolates still continues to have extensive synthetic applications.[4] Well-established examples of the latter are the Evans α-amino acid derived *N*-acyloxazolidinones[5] and the Oppolzer's *N*-acylcamphorsultam derivatives.[6] High diastereofacial selectivities have also been attained in aldol reactions using chiral α-oxy and/or α-amino ketone enolates.[7] In these instances (Figure 1), however, the access to the desired α-substituted *β*-hydroxy carboxylic acids involves the destruction of the source of chiral information at a later stage.[7,8] In addition, although both the carboxylic acid derived enolate and the α-oxy ketone enolate methodologies have proven to be very effective for "propionate" aldol reactions, the insufficient stereoselectivity generally attained in "acetate" aldol reactions still continues to be a problem.[9] Recent research in this laboratory[10] has led to the design of the lithium enolate of the methyl ketone **4** (Scheme 1) that helps to solve these limitations. The main distinguishing features of our model are, firstly, the use of camphor and acetylene, vide infra, as the inexpensive and readily available starting materials for the preparation of the methyl ketone reagent, secondly, the high diastereoselectivities attained in "acetate" aldol reactions and, finally, an easy post-reaction/final recovery of the starting

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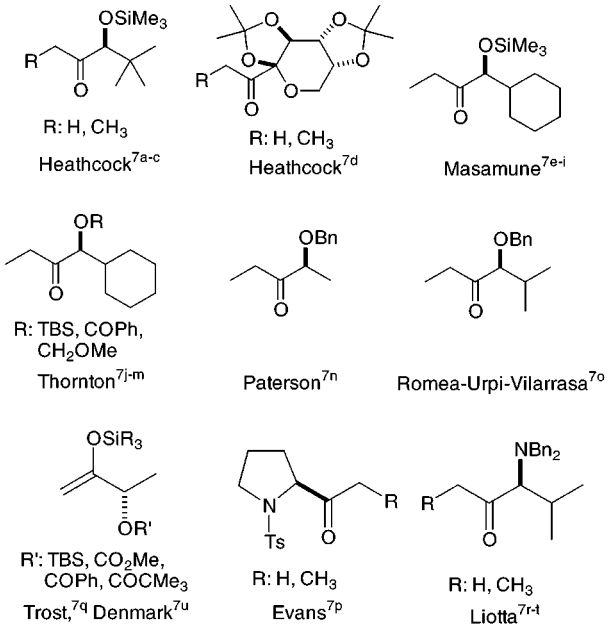
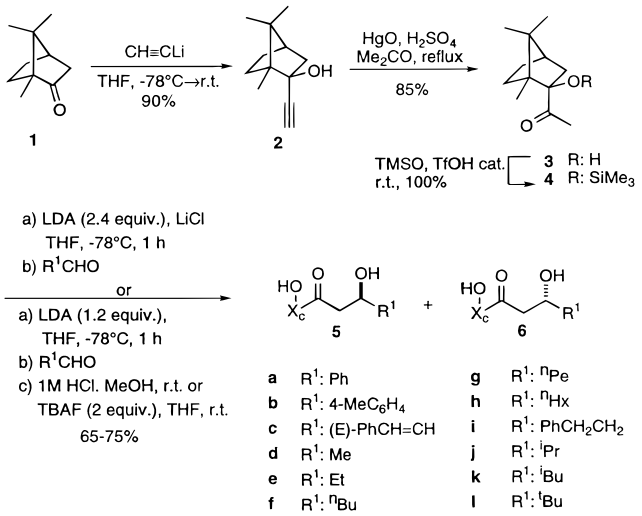



**Figure 1.** Array of chiral nonracemic α′-amino and α′-oxy ketones developed for asymmetric aldol reactions. TBS: *tert*-butyldimethylsilyl.

camphor that enables its reuse as the chiral controller of the process. In this way the method appears to have

**Scheme 1**




potential applicability for scaling-up and, formally, it involves the conversion of acetylene[11] into *β*-hydroxy carboxylic acids, ketones, and aldehydes. Herein, we present further evidence of the powerful ability of this lithium enolate model to transfer chiral information in those aldol reactions that inherently have particularly poor diastereofacial selectivity.[12]

## Results and Discussion

As we have previously reported,[10] reactions between the lithium enolate of **4** (Scheme 1) and some representative aldehydes yielded the corresponding aldol products with remarkably high diastereoselectivity. The diastereomeric ratio of the product was unchanged after desilylation to afford the adducts **5**/**6**, typically 95:5 (Table 1). In every case, the reactions were conducted at −78 °C by addition of a precooled (−78 °C) THF solution of the respective aldehyde (2−3 equiv) to the previously generated lithium enolate of **4**. The latter was generated at −78 °C in dry THF using lithium diisopropylamide (LDA). We have now found that freshly generated LDA is the most effective amide base compared with both potassium bis(trimethylsilyl)amide (KHMDS) and sodium bis(trimethylsilyl)amide (NaHMDS). Thus, whilst the treatment of benzaldehyde with the enolate generated from **4** and KHMDS afforded the corresponding dehydrated enone, the same aldehyde upon treatment with the enolate generated by using NaHMDS led to the expected aldol adduct with a low 50% yield. At this point it was our concern to investigate whether it is necessary or not to have the trimethylsilyl group attached to the α-hydroxy function in **4**. If aldol reactions conducted with the lithium enolate of **3** afforded similar results, it would demonstrate the inherent ability of this particular model. In this regard, prior studies have established that the size of the α-OR group is one of the main stereochemical control elements in lithium-mediated ketone aldol reactions.[7j−n,o] It has also been found that aldol reactions

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**Table 1. Effect of the Metal Counterion upon the Diastereoselectivity of the Aldol Reaction of the Enolate of 3 and 4 with Representative Aldehydes[a]**

| entry | aldehyde | lithium enolate of | additive[b] (equiv) | selectivity ratio **5**:**6**[c] | yield (%)[d,e] |
|---|---|---|---|---|---|
| 1 | $C_6H_5CHO$ | **4** | | 96:4 | 80 (100:0) |
| 2 | | **3** | | 72:28 | 86 (100:0) |
| 3 | | **3** | $MgBr_2$ (2.2) | 86:14 | 70 (85:15) |
| 4 | | **4** | $AlMe_2Cl$ (1.2) | 33:67 | ND (80:20) |
| 5 | | **3** | $AlMe_2Cl$ (2.4) | 50:50 | ND (40:60) |
| 6 | | **4** | $Ti(O^iPr)_3Cl$ (4.0) | 25:75 | ND (50:50) |
| 7 | | **3** | $Ti(O^iPr)_3Cl$ (4.0) | 15:85 | 30 (100:0) |
| 8 | 4-$CH_3C_6H_4CHO$ | **4** | | 96:4 | 67 (85:15) |
| 9 | | **3** | | 84:16 | ND (85:15) |
| 10 | $PhCH_2CH_2CHO$ | **4** | | 95:5 | 85 (100:0) |
| 11 | | **3** | | 75:25 | ND (100:0) |
| 12 | *i*-$C_3H_7CHO$ | **4** | | 97:3 | 67 (100:0) |
| 13 | | **3** | | 86:14 | 81 (100:0) |
| 14 | | **3** | $ZnCl_2$ (2.2) | 88:12 | 72 (85:15) |
| 15 | $(CH_3)_2CHCH_2CHO$ | **4** | | 96:4 | 75 (95:5) |
| 16 | | **3** | | 89:11 | ND (70:30) |
| 17 | | **3** | $Ti(O^iPr)_3Cl$ (4.0) | 25:75 | 71 (100:0) |

[a] Reactions conducted at −78 °C on a 0.5 mmol scale by adding the aldehyde to the corresponding enolate in THF. [b] Mg and Zn enolates were prepared by transmetalation of the Li enolate with dry $MgBr_2$ or $ZnCl_2$, respectively, for 1 h at −78 °C; Ti and Al enolates were prepared by transmetalation of the Li enolate with $Ti(O^iPr)_3Cl$ or $AlMe_2Cl$, respectively, for 1.5 h at −30 °C. [c] Ratios determined by $^{13}C$ NMR analysis of the reaction crudes. [d] Values in parentheses represent the ratio product:starting ketone. [e] Combined yields of both compounds **5** and **6** after purification of the crude product by column chromatography (eluant ethyl acetate:hexane); ND, not determined.

involving the metal enolates of α-hydroxy ethyl ketones provided substantially lower levels of diastereoselectivity than those involving the respectively more sterically demanding α-trimethylsilyloxy derivatives.[8a] On the basis of these precedents, it was not a surprise to observe that the lithium enolate of **3**, generated at −78 °C with 2 equiv of LDA in THF as solvent, reacted with benzaldehyde and 4-methylbenzaldehyde to provide the corresponding aldols with significantly lower selectivities compared with those achieved with the lithium enolate of **4**. For example, as Table 1 shows, the diastereomeric ratio of aldols dropped from 96:4 to 72:28 for the first case (Table 1, entries 1 and 2) and from 96:4 to 84:16 for the latter (Table 1, entries 8 and 9). The same trend was observed in reactions of the lithium enolate **3** with aliphatic aldehydes such as hydrocinnamaldehyde (Table 1, entries 10 and 11), isobutyraldehyde (Table 1, entries 12 and 13), and isovaleraldehyde (Table 1, entries 15 and 16). Attempts to improve the results obtained with **3** through transmetalation of its lithium enolate with $MgBr_2$, $AlMe_2Cl$, and $ZnCl_2$ were unsuccessful. Of interest, however, the transmetalation of the organolithium derived from **3**, generated as above, with a 4-fold excess of $Ti(O^iPr)_3Cl$ according to Reetz and Peter[13] and subsequent reaction with benzaldehyde led to **5a**/**6a** in a ratio of 15:85 (Table 1, entry 7). Under the same conditions, isovaleraldehyde gave **5k**/**6k** in a ratio of 25:75 (Table 1, entry 17). In both cases, although the chemical yield and the attained diastereoselectivity were low, a reversal in the ratio of isomers was observed.

These discouraging results attained with the lithium enolate of **3** could, however, be dramatically improved by the presence of lithium chloride in the reaction.[14] In this regard, recent structural studies by Williard[14d] have provided some key elements for the understanding of the role that lithium halides play in the shape of the aggregates formed in solution.[15] From those studies, the conclusion is that a greater degree of asymmetric induction can be predicted for the aldol reactions carried out in the presence of a lithium halide salt. Table 2 summarizes the results achieved when the lithium enolate of **3**, generated as above but in the presence of a 6-fold excess of LiCl, was treated with the respective precooled aldehyde. As can be seen, the predicted enhancement of the diastereoselectivity occurred in essentially all the examples tested. When benzaldehyde was employed

**Table 2. Aldol Reaction of the Lithium Enolate of 3 with Representative Aldehydes in the Presence of LiCl[a]**

| entry | aldehyde | selectivity ratio[b] **5**:**6** | yield **5** (%)[c] |
|---|---|---|---|
| 1 | $C_6H_5CHO$ | 88:12 | 67 |
| 2 | 4-$CH_3C_6H_4CHO$ | 93:7 | 76 |
| 3 | $C_6H_5$-CH=CH-CHO | 89:11 | 71 |
| 4 | $CH_3CHO$ | 96:4 | 70[d] |
| 5 | $CH_3CH_2CHO$ | 93:7 | 65 |
| 6 | $CH_3(CH_2)_3CHO$ | 94:6 | 61 |
| 7 | $CH_3(CH_2)_4CHO$ | 94:6 | 60[d] |
| 8 | $CH_3(CH_2)_5CHO$ | 91:9 | 65 |
| 9 | $C_6H_5CH_2CH_2CHO$ | 88:12 | 75 |
| 10 | *i*-$C_3H_7CHO$ | 95:5 | 67 |
| 11 | $(CH_3)_2CHCH_2CHO$ | 93:7 | 75 |
| 12 | $(CH_3)_3CCHO$ | >98:2 | 70 |

[a] Reactions conducted at −78 °C on a 0.5 mmol scale by adding a precooled (−78 °C) solution of the aldehyde in THF to the lithium enolate of **3** and 6-fold excess of LiCl in the same solvent. [b] Ratios determined by both $^{13}C$ NMR and HPLC analysis of the reaction crudes. [c] Yields of pure compound **5** after purification of the crude product by column chromatography and separation of diastereomers by HPLC (Merck LiChrosorb Si 60 7 μm column, eluant ethyl acetate:hexane). [d] Yields of the mixture of both isomers **5** and **6** after purification of the crude product by column chromatography.

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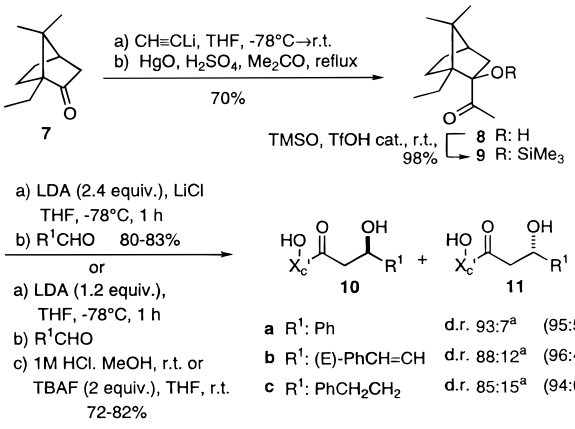
**Scheme 2**




[a] Diastereomeric ratios from the enolate of **8**. [b] Diastereomeric ratios from the lithium enolate of **9**.

(entry 1 in Table 2), the stereoselectivity ratio **5a**/**6a** was slightly lower (88:12) compared to that attained with the enolate of **4** (96:4, entry 1 in Table 1). However, nearly the same stereoselectivity was observed when isobutyraldehyde was used (entry 10 in Table 2, and entry 12 in Table 1). Several other aldehydes were successfully employed in the present asymmetric aldol reaction.[16] In all but three cases, the respective aldols **5**/**6** were produced with almost the same level of diastereoselectivity as that achieved from the lithium enolate of **4**. From the data in the Table 2, it is evident that the reaction diastereoselectivity is independent of the nature of the aldehyde. This shows generality for aromatic, α,*β*-unsaturated and linear as well as branched chain aliphatic aldehydes. In every case, the diastereomeric ratios were determined primarily by integration of the $^{13}C$ NMR signals corresponding to the newly generated carbinol carbon, which are easily distinguishable for both diastereomers in the 65−75 ppm region. To ensure the validity of this measurement assay, each crude mixture was also analyzed by HPLC, where the major isomer always shows a longer retention time. In all cases, the diastereomeric ratios measured by both techniques were essentially equivalent. Next, we prepared the parent hydroxy and silyloxy ketones **8** and **9** by following, from **7**, the same reaction sequence as that employed for the preparation of **3** and **4** from camphor. Ketones **8** and **9** exhibit a sterically more congested environment due to the presence of the ethyl group at the bridge instead of methyl. However, as Scheme 2 illustrates, the aldol reaction of the lithium enolate of either **8** or **9** with three representative aldehydes afforded adducts **10**/**11** with almost the same level of diastereoselectivity as that attained in the reaction of the lithium enolates of **3** and **4** with the same aldehydes. Although we have not carried out any specific investigation of the mechanism of this aldol reaction, the Zimmerman−Traxler-type[17,18] transition state depicted in Figure 2 would nicely account for the observed stereochemical course. In such a transition state, which for

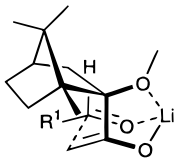
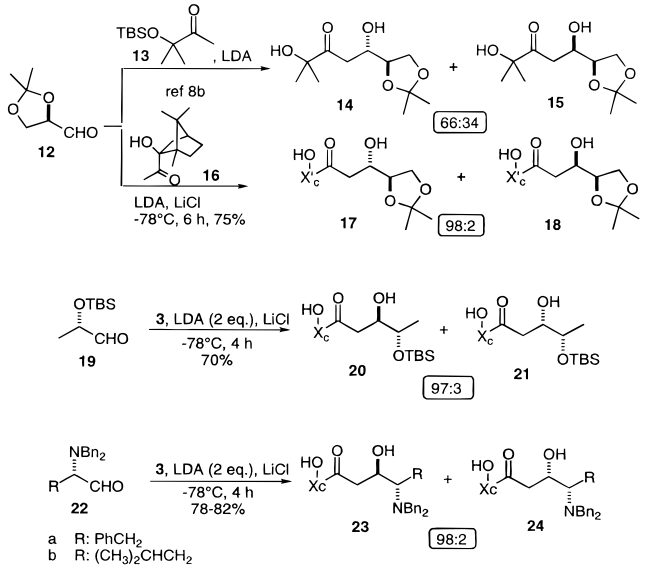


**Figure 2.** A simplified transition state that accounts for the formation of the major aldol adduct **5**.

**Scheme 3**




simplification does not consider aggregation, the internal chelation between lithium and both the enolate and the silyloxy oxygens fixes the conformation of the enolate in such a way that *π*-facial discrimination across the enolate plane is very efficient. Thus, the aldehyde would preferentially approach the enolate from its less-shielded rear side with the $R^1$ group in an equatorial-like arrangement.

**Double Asymmetric Induction.** To provide further insight into the ability of our model to transfer chiral information in reactions of poor diastereofacial selectivity, we next examined the concept of double asymmetric induction[19] (Scheme 3) in reactions of both the methyl ketones **3** and **16**, the latter prepared from (*S*)-camphor, with either chiral (*R*)- or (*S*)-α-oxy and α-amino aldehydes. The reaction of the aldehyde (*R*)-**12** with the enolate of **13** is reported by Heathcock[8b] to afford a mixture of aldols **14**/**15** in a ratio of 66:34, while the enolate of **16** upon treatment with (*R*)-**12** gave **17**/**18** in a ratio of 98:2. Thus, in this case, where both reactants are in a matched relationship, the preferred facial selectivity of the enolate reinforces notably the preferred selectivity of the aldehyde, which results in the almost exclusive formation of **17**. Likewise, when (*S*)-**19** was allowed to react with the lithium enolate of **3**, where the sense of asymmetric induction of both chiral reactants was also matched, a mixture of diastereomeric aldols **20**/**21** was obtained in a ratio of 97:3. The major isomer **20** was then separated by column chromatography as a white solid in 75% yield and submitted to a single crystal X-ray structure analysis to confirm the assigned configuration for the adduct. The same trend in stereoselec-

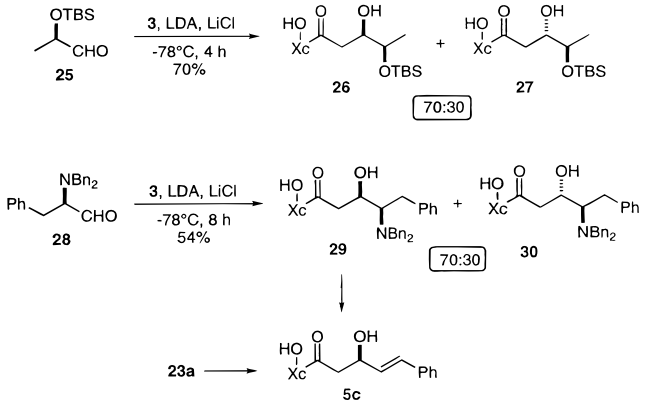
(16) For these reactions we have systematically employed a 6-fold excess of LiCl. Nonetheless, we have found that as little as 3-fold excess of LiCl, but not less, provides the same effect on diastereoselectivity.

(17) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(18) For transition structures involved in aldol reactions of lithium enolates, see: Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.

(19) For a review on double asymmetric induction, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

**Scheme 4**

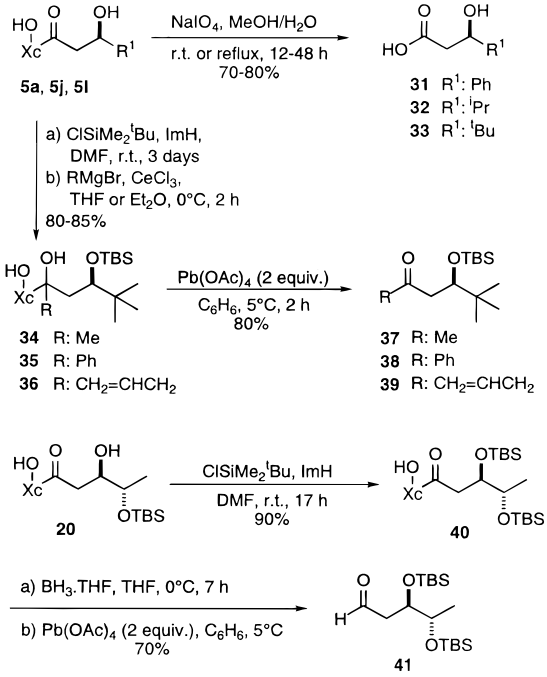



tivity was observed for the reactions between the lithium enolate of **3** and the α-amino aldehydes (*S*)-**22a** and (*S*)-**22b** to give the respective aldols **23a** and **23b** essentially as single diastereomers. Unfortunately, the present model provides unsatisfactory levels of diastereoselectivity when both chiral reactants are mismatched. For instance, the reaction of the lithium enolate of **3** with (*R*)-**25** (Scheme 4) exhibits opposing aldehyde and enolate selectivities, leading to a mixture of **26**/**27** in a diastereomeric ratio of 70:30. The major isomer **26** was isolated in 40% yield by column chromatography and submitted to a single crystal X-ray structure analysis to unequivocally determine the sense of asymmetric induction for the major isomer. The configurational assignment for the minor adduct **27** was done by comparison of its $^1$H NMR spectrum with those corresponding to isomers **20** and **21**, which allowed the latter structures to be excluded. From the assignments it is clear that the production of these isomer distributions is due to the diastereoselectivity inherent to those aldol reactions rather than to an isomerization of the aldehydes under the reaction conditions used. In a similar way, the aldehyde (*R*)-**28**, upon treatment with the enolate **3**, provided a mixture of **29**/**30** in a ratio of 70:30. In this case, the configuration for the major isomer was established by conversion of both **29** and **23a** into the same compound **5c**, which was identical to that obtained by the aldol reaction using cinnamaldehyde, vide supra.

**Preparation of *β*-Hydroxy Carbonyl Compounds.** As we had anticipated the oxidative cleavage of the acyloin moiety in the aldol adducts provided the corresponding *β*-hydroxy carboxylic acids along with the starting camphor, which could be recovered and reemployed. For example, as shown in Scheme 5, when **5a**, **5j**, and **5l** were submitted to treatment with sodium periodate in methanol−water, compounds **31**, **32**, and **33** were isolated in yields of 70%, 80% and 75%, respectively. In every case, the starting camphor (Aldrich, $[\alpha]_D^{25} = +42.2$ ($c = 1$, EtOH)) was easily recovered (recovered material, $[\alpha]_D^{25} = +41.5$ ($c = 1$, EtOH)) in yields of 85−90% by simple aqueous work-up. Comparison of the optical rotations of these *β*-hydroxy acids with those previously described in the literature confirmed the stereochemical assignments for the adducts. In addition, a single crystal X-ray analysis of the starting aldol **5l** corroborated the assigned configuration for the adducts.

Problems arose, however, when we attempted the preparation of *β*-hydroxy ketones through an organometallic addition−diol cleavage sequence. In these instances,

**Scheme 5**




the addition reaction of either Grignard or lithium reagents to the carbonyl group of the corresponding aldol products failed. Fortunately, by using organocerium reagents,[20] we found that we could prepare the carbinols **34**, **35**, and **36** in 85%, 90%, and 80%, yields, respectively. Although these addition reactions proceeded with good diastereoselectivity, as judged by the $^1$H NMR spectra of the resulting mixture of carbinols, they were neither isolated nor characterized. Instead, each crude compound was submitted to oxidative cleavage by treatment with lead tetraacetate in benzene to give the *β*-hydroxy ketones **37**, **38**, and **39**, each in 80% yield. In a similar way, the diborane reduction of the keto group in the TBS-protected aldol **40**, which was obtained by standard silylation of **20**, followed by oxidative work-up with lead tetraacetate provided the α-unsubstituted *β*-silyloxy aldehyde **41** in 70% yield along with the recovery of the starting camphor in 80% yield.[21]

## Conclusions

The present study shows that the acetyl group attached to the camphor moiety in the way delineated in Scheme 1 acts as a powerful "acetate" equivalent for aldol reactions of inherently poor diastereofacial selectivity. Particularly noteworthy are the results achieved with the methyl ketone **3** in the presence of a 6-fold excess of LiCl, which are almost the same as those attained with the more sterically biased methyl ketone **4**. This case represents the first example of highly diastereoselective aldol reactions involving the lithium enolate of α-hydroxy methyl ketones. Significantly, the procedure does not destroy the auxiliary during work-up, and it can be recovered. Therefore, the method is economically viable for the preparation of α-unsubstituted *β*-hydroxy car-

(20) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(21) For a recent paper dealing with the one- or two-step synthesis of ketones and aldehydes from *N*-acylbornane-10,2-sultam derivatives, see: Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; De Brabander, J. *Helv. Chim. Acta* **1997**, *80*, 1319.

boxylic acids, ketones, and aldehydes not only by using the cheap (+)-(1*R*)-camphor but also the non-natural (−)-(1*S*)-isomer. Further applications of this enolate model will be reported in the near future.[22]

## Experimental Section

**General.** Melting points were determined with capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (200 MHz) spectra and $^{13}C$ spectra (50 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as $\delta$ values (ppm) relative to residual $CDCl_3$ $\delta_H$ (7.26 ppm) and $CDCl_3$ $\delta_C$ (77.0 ppm) as internal standards, respectively. Optical rotations were measured at 25 ± 0.2 °C. Enantiomeric excesses were determined by comparison with racemic standards using chiral HPLC (CHIRALPAK-AS 250 × 4.6 mm column; eluant $^i$PrOH/hexane 50:50; accuracy ±0.1%) with flow rates of 0.5 mL/min and using a DAD (254 nm). Flash chromatography was executed with Merck Kiesegel 60 (230−400 mesh) using mixtures of EtOAc and hexane as eluants. THF was distilled over sodium and benzophenone (indicator). X-ray structure analyses of compounds **3**, **5l**, **20**, and **26** were performed by one of us (A.L.).[23]

**(1*R*)-2-*endo*-Acetyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (*endo*-2-acetylisoborneol) (3).** An oven-dried, 1 L, three-necked round-bottomed flask equipped with a thermometer and a magnetic stirrer bar was flushed with nitrogen, charged with THF (400 mL), and cooled to −78 °C. Butyllithium (2.5 M in hexane, 100 mL, 250 mmol) was added using a syringe, and dry acetylene was blown over the yellow solution held below −70 °C for 45 min.[24] (*R*)-(+)-Camphor (15.23 g, 100 mmol) was then added over the clear solution of lithium acetylide at the same temperature. After the addition, the cold bath was removed and the mixture was stirred overnight at room temperature. The flask was opened to the atmosphere, and 1 M HCl (100 ml) was added slowly. The quenched reaction was stirred for 1 h, and then the solvent was removed at reduced pressure. $CH_2Cl_2$ (200 mL) was added, and the mixture was transferred to a separatory funnel. The aqueous layer was separated and the organic layer was washed with 1 M HCl. The combined aqueous layers were extracted with $CH_2Cl_2$, the combined organic extracts were washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give a mixture of ethynyl carbinols, endo:exo 97:3, as a dark oil. This crude material was dissolved in acetone (1.3 L) and added dropwise over a period of 1.5 hours to a warmed (60 °C) mixture prepared previously as follows: In a three-necked round-bottomed flask, equipped with a reflux condenser, a magnetic stirrer bar and a dropping funnel, red mercuric oxide (1.32 g) was dissolved in a solution of concentrated sulfuric acid (2.1 mL), water (53 mL), and acetone (260 mL). The resulting reaction mixture was stirred at 60 °C for an additional 15 min and allowed to cool. A saturated aqueous solution of $NaHCO_3$ (250 mL) was added to the reaction mixture, the solvent was removed under reduced pressure and $CH_2Cl_2$ (250 mL) was added. The aqueous layer was separated, and the organic layer was washed with saturated solution of $NaHCO_3$. The combined aqueous layers were extracted with $CH_2Cl_2$, and the organic extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the solid crude product was purified by crystallization from hexane: yield 17.6 g, 90%, mp 90−95 °C; $[\alpha]_D^{25} = -65.6$ ($c$ =1.0, $CH_2Cl_2$); IR (KBr) $\upsilon$ 3421, 1690 cm$^{-1}$; $^1$H NMR ($CDCl_3$, $\delta$) 0.83 and 0.92 (s, 3H), 1.03−0.95 (m, 1H), 1.08 (s, 3H), 1.27−1.15 (m, 1H) 1.49−1.34 (m, 1H), 1.74−1.65 (m, 1H), 1.90−1.81 (m, 2H), 2.25 (s, 3H), 2.14−2.29 (m, 1H), 2.65 (s, 1H); $^{13}$C NMR ($CDCl_3$, $\delta$) 10.5, 20.3, 20.8, 26.4, 27.6, 30.1, 40.9, 45.0, 50.3, 52.1, 87.4, 211.8. Anal. Calcd for $C_{12}H_{20}O_2$ (196.32): C, 73.41; H, 10.29. Found: C, 73.06; H, 10.32.

**(1*R*)-2-*endo*-Acetyl-1-ethyl-7,7-dimethylbicyclo[2.2.1]-heptan-2-ol (8).** Exactly the same two-step procedure described above was employed starting from ketone **7**[25] (16.6 g, 100 mmol). The resulting crude product (endo:exo ratio 95:5) was purified by column chromatography (eluant EtOAc/hexane 1:10) to afford 14.7g (70%) of the title compound: mp 45 °C; $[\alpha]_D^{25} = -84.9$ ($c$ = 1.0, $CH_2Cl_2$); IR (KBr) $\upsilon$ 3446, 1684 cm$^{-1}$; $^1$H NMR ($CDCl_3$, $\delta$) 0.73 (t, $J$ = 7.7 Hz, 3H), 0.86 and 1.09 (s, 3H), 1.20−1.91 (m, 9H), 2.31 (s, 3H), 3.62 (s, 3H); $^{13}$C NMR ($CDCl_3$, $\delta$) 9.8, 18.5, 21.0, 21.1, 26.0, 26.6, 27.7, 43.0, 45.5, 51.0, 57.1, 87.5, 214.7. Anal. Calcd for $C_{13}H_{22}O_2$ (210.31): C, 74.24; H, 10.54. Found: C, 74.30; H, 9.83.

**General Procedure for the Silylation of 3 and 8.**[26] To a mixture of the corresponding hydroxy ketone (10 mmol) and 3-trimethylsilyl-2-oxazolidinone TMSO (2.32 ml, 15 mmol) under a nitrogen atmosphere was added one drop of trifluoromethanesulfonic acid. The reaction mixture was stirred at room temperature for 1 h. $CH_2Cl_2$ (25 ml) was then added, and the resulting solution was washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Hexane (15 mL) was added to the oily residue, and the resulting white solid was filtered and washed with additional hexane (15 mL). The solvent was evaporated, and the crude product was purified by column chromatography (eluant EtOAc/hexane 1:10).

**(1*R*)-2-*endo*-Acetyl-2-*exo*-(trimethylsilyloxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (4):** yield 2.68 g, 100%, mp 38 °C; $[\alpha]_D^{25} = -24.9$ ($c$ = 1.0, $CH_2Cl_2$); IR (KBr) $\upsilon$ 1708 cm$^{-1}$; $^1$H NMR ($CDCl_3$, $\delta$) 0.06 (s, 9H), 0.76−0.08 (m, 1H), 0.80, 0.98 and 1.03 (s, 3H), 1.11−1.05 and 1.40−1.26 (m, 1H), 1.57 (s, 1H), 1.77−1.69 (m, 2H), 2.15 (s, 3H), 2.51−2.45 (m, 1H); $^{13}$C NMR ($CDCl_3$, $\delta$) 1.7, 11.4, 20.3, 21.0, 25.8, 26.9, 30.1, 39.7, 45.3, 50.9, 51.6, 90.7, 209.3. Anal. Calcd for $C_{15}H_{28}O_2Si$ (268.52): C, 67.09; H, 10.53. Found: C, 66.75; H, 10.56.

**(1*R*)-2-*endo*-Acetyl-2-*exo*-(trimethylsilyloxy)-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptane (9):** yield 2.45 g, 98%, colorless oil; $[\alpha]_D^{25} = -41.2$ ($c$ = 2.0, $CH_2Cl_2$); IR (KBr) $\upsilon$ 1705 cm$^{-1}$; $^1$H NMR ($CDCl_3$, $\delta$) 0.06 (s, 9H), 0.87 (s, 3H), 0.90 (t, $J$ = 7.8 Hz, 3H), 1.08 (s, 3H), 1.77−1.52 (m, 7H), 2.16 (s, 3H), 2.44 (d, $J$ = 12.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$, $\delta$) 1.5, 10.8, 18.7, 20.7, 22.1, 25.3, 26.0, 27.0, 40.5, 45.9, 51.5, 54.5, 91.8, 210.1.

**General Procedure for Aldol Reactions of 3 and 8 with Aldehydes.** A mixture of diisopropylamine (0.33 mL, 2.4 mmol) and anhydrous LiCl (0.25 g, 6 mmol) in dry THF (3 mL) was cooled to −78 °C under a nitrogen atmosphere and *n*-butyllithium (1.6 M in hexane, 1.5 mL, 2.4 mmol) was added dropwise. After 30 min of stirring at the same temperature, a solution of **3** (0.20 g, 1 mmol) or **8** (0.21 g, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was allowed to stir for 1 or 2 h, respectively, at −78 °C, and then a precooled (−78 °C) solution of the corresponding aldehyde (2.0 mmol) in THF (10 ml) was added dropwise. The reaction was allowed to stir from 1−7 h at −78 °C and then was quenched with 5 mL of saturated aqueous solution of $NH_4Cl$. The resulting mixture was allowed to warm to room temperature, after which the layers were separated, and the aqueous layer was extracted twice with $CH_2Cl_2$. The combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the corresponding aldol product as a clear to

(22) Another paper will deal with the use of **4** for the asymmetric Mannich-type reaction, see: Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem. Int. Ed.*, in press.

(23) Crystallographic data (excluding structure factors) for the structure of **26** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101850. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax (+44) 1223 336-033; email deposit@ccdc.cam.ac.uk). For crystallographic data of the structure **3**, **5l**, and **20**, see ref 10.

(24) Midland, M. M.; McLoughlin, J. I.; Werley, R. T., Jr. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, p 391.

(25) Fischer, N.; Opitz, G. *Organic Syntheses:* Wiley: New York, 1973; Collect. Vol. 5, p 877.

(26) Aizpurua, J. M.; Palomo, C.; Palomo, A. L. *Can. J. Chem.* **1984**, *62*, 336.

light yellow oil. The diastereomeric ratio was determined in each case by HPLC and $^{13}C$ NMR analyses of the respective crude product. Purification was effected by flash column chromatography, using a 1:15 EtOAc−hexane mixture as the eluant and then by preparative HPLC, except for the mixtures **5d**/**6d** and **5g**/**6g**.

**General Procedure for Aldol Reactions of 4 and 9 with Aldehydes.** A mixture of diisopropylamine (0.16 mL, 1.2 mmol) in THF (3 mL) was cooled to −78 °C, and *n*-butyllithium (1.6 M in hexane, 0.75 ml, 1.2 mmol) was added dropwise. After 30 min of stirring, a solution of **4** (0.27 g, 1 mmol) or **9** (0.25 g, 1 mmol) in THF (2 mL) was added dropwise. The mixture was allowed to stir for 1 or 2 h, respectively at −78 °C, and then the precooled aldehyde (2.0 mmol) was added dropwise. The reaction mixture was allowed to stir for 3−8 h at −78 °C, and then the reaction was quenched with 5 mL of saturated aqueous $NH_4Cl$. The resulting mixture was allowed to warm to room temperature, after which the layers were separated and the aqueous layer was extracted twice with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue thus obtained was desilylated by either one of the procedures that follows with essentially same yield: (A) It was dissolved in MeOH (4 mL) and after the addition of 1 N HCl (2 mL) the mixture was stirred at room temperature for 3 h. $CH_2Cl_2$ (20 mL) was added, the organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. Purification was effected by flash column chromatography, using a 1:15 EtOAc−hexane mixture as the eluant and then by preparative HPLC. (B) The residue was dissolved in THF (3 mL), and after the addition of anhydrous 1 M TBAF in THF (2 mL), the mixture was stirred at room temperature for 5 min. Evaporation of solvent and purification by column chromatography afforded the aldol products as clear to light yellow oils. The diastereomeric ratio was determined in each case by HPLC and $^{13}C$ NMR analyses of the respective unpurified product.

**Data for 5a:** yield 0.20 g, 67%, colorless oil purified by preparative HPLC; $[\alpha]_D^{25} = +35.3$ ($c = 1.0$, $CH_2Cl_2$); IR (film) $\upsilon$ 3427, 1702 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 0.82, 0.94 and 1.11 (s, 3H), 1.45−1.15, 1.75−1.62 and 1.83−1.77 (m, 2H), 2.30 (m, 1H), 2.55 (dd, $J = 2.2$ Hz, $J' = 10.2$ Hz, 1 H), 7.36−7.24 (m, 5H); $^{13}C$ NMR ($CDCl_3$, $\delta$) 11.3, 20.6, 20.9, 26.3, 30.3, 41.4, 45.1, 48.2, 50.0, 51.8, 71.3, 87.8, 125.6, 128.3, 143.3, 212.2.

**Data for 5j:** yield 0.18 g, 67%, mp 53−54 °C; $[\alpha]_D^{25} = +19.6$ ($c = 0.51$, $CH_2Cl_2$); IR (KBr) $\upsilon$ 3382, 1692 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 0.85 (s, 3H), 0.92 and 0.95 (d, $J = 3.2$ Hz, 3H), 0.98 and 1.13 (s, 3H), 1.46−1.17 (m, 2H), 1.86−1.56 (m, 5H), 2.28 (m, 1H), 2.41 (dd, $J = 2.2$ Hz, $J' = 15.4$ Hz, 1H), 2.98 (dd, $J = 10.4$ Hz, $J' = 15.4$ Hz, 1H), 3.33−3.32 ($s_b$, 1H), 3.80 (ddd, $J = 2.2$ Hz, $J' = 10.4$ Hz, $J'' = 5.5$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$, $\delta$) 11.2, 17.8, 18.3, 20.6, 20.9, 26.2, 30.3, 33.6, 41.3, 42.7, 45.1, 50.9, 51.8, 73.8, 87.8, 213.8. Anal. Calcd for $C_{16}H_{28}O_3$ (268.44); C, 71.58; H, 10.53. Found: C, 71.20; H, 10.57.

**Data for 5l:** yield 0.20 g, 70%, mp 73−74 °C; $[\alpha]_D^{25} = +21.7$ ($c = 0.51$, $CH_2Cl_2$); IR (KBr) $\upsilon$ 3404, 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 0.83 (s, 3H), 0.90 (s, 9H), 0.96 and 0.11 (s, 3H), 1.45−1.17, 1.70−1.61 and 1.84−1.73 (m, 2H), 2.25 (m, 1H), 2.38 (dd, $J = 2.2$ Hz, $J' = 14.8$ Hz, 1H), 2.7 ($s_b$, 1H), 2.96 (dd, $J = 10.6$ Hz, $J' = 14.8$ Hz, 1H); 3.4 ($s_b$, 1H), 3.67 (dd, $J = 2.2$ Hz, $J' = 3.0$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$, $\delta$) 11.2, 20.4, 20.7, 25.5, 25.6, 30.2, 34.5, 40.4, 41.2 44.9, 50.8, 51.5, 76.6, 87.7, 213.8. Anal. Calcd for $C_{17}H_{30}O_3$ (282.47); C, 72.28; H, 10.73. Found: C, 71.95; H, 10.77.

**Data for 10a:** yield 0.21 g, 66%, mp 103 °C; $[\alpha]_D^{25} = +35.6$ ($c = 0.51$, $CH_2Cl_2$); IR (KBr) $\upsilon$ 3374, 1687 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 0.74 (t, $J = 7.6$ Hz, 3H), 0.88 and 1.14 (s, 3H), 1.20−1.90 (m, 9H), 2.02 (d, $J = 13$ Hz, 1H), 2.65 (dd, $J = 2.8$ Hz, $J' = 14.9$ Hz, 1H); 3.24−3,23 (m, 1H), 3.42 (dd, $J = 10.3$ Hz, $J' = 14.9$ Hz, 1H); 3.69 (s, 1H) 5.09−5.03 (m, 1H), 7.39−7.25 (m, 5H); $^{13}C$ NMR ($CDCl_3$, $\delta$) 10.3, 14.1, 18.4, 21.1, 21.5, 22.6, 25.8, 26.3, 31.6, 44.5, 45.7, 48.7, 51.8, 57.6, 72.4, 87.9, 125.6, 127.9, 128.6, 143.1, 216.4. Anal. Calcd for $C_{20}H_{28}O_3$ (316.14): C, 75.90; H, 8.92. Found: C, 75.90; H, 8.4.

**Data for 20:** yield 0.27 g, 70%, mp 89−91 °C; $[\alpha]_D^{25} = +13.0$ ($c = 1.02$, $CH_2Cl_2$); IR (KBr) $\upsilon$ 3400, 1638 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 0.05 and 0.07 (s, 3H), 0.82 (s, 3H), 0.86 (s, 9H), 0.97 and 1.20 (s, 3H), 1.17 (d, $J = 6.0$ Hz, 3H), 1.43−1.17, 1.67−1.59 and 1.81−1.74 (m, 2H), 2.28 (m, 2H), 3.10 ( dd, $J = 8.0$ Hz, $J' = 14.0$ Hz, 1H); 3.31 and 3.62 (s, 1H), 3.85 (m, 2H); $^{13}C$ NMR ($CDCl_3$, $\delta$) −4.7, −4.5, 11.2, 18.1, 18.8, 20.5, 20.9, 25.8, 26.2, 30.3, 40.2, 41.2, 45.1, 50.9, 51.7, 71.6, 73.6, 87.8, 213.3. Anal. Calcd for $C_{21}H_{40}O_4Si$ (384.70); C, 65.56; H, 10.50. Found: C, 65.32; H, 10.45.

**General Procedure for the Oxidation of Aldol Products.** To a solution of the corresponding aldol **5** (1 mmol) in methanol (6.6 mL) was added a solution of sodium periodate (2.14 g, 10 mmol) in water (3.3 mL). The mixture was allowed to stir at room temperature or at reflux until disappearance of the starting material as monitored by TLC (EtOAc−hexane 1:3). The solvent was evaporated, the solid residue was dissolved in a minimum amount of water, and the resulting solution was extracted twice with $Et_2O$. the combined ethereal extracts were washed with 2 N NaOH, dried over $MgSO_4$, filtered, and the solvent was evaporated to afford the starting (*R*)-(+)-camphor in 85−90% yield. The basic aqueous layer was first acidified by adding concentrated HCl and then extracted with $Et_2O$. The combined extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford the corresponding $\beta$-hydroxy acid in 70−80% yields.

**Data for 31:** yield 0.12 g, 70%; $[\alpha]_D^{25} = +15.5$ ($c = 0.9$, EtOH); (lit.[27] $[\alpha]_D^{25} = +17.9$ ($c = 2.3$, EtOH 95%)); IR (KBr) $\upsilon$ 3510, 1711 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 2.77 (dd, $J = 3.9$ Hz, $J' = 16.8$ Hz, 1H), 2.85 (dd, $J = 8.7$ Hz, $J' = 16.5$ Hz, 1H), 5.16 (dt, $J = 8.7$, $J' = 3.9$ Hz, 1H), 7.31−7.12 (m, 5H); $^{13}C$ NMR ($CDCl_3$, $\delta$) 42.7, 70.2, 125.7, 128.1, 128.7, 142.2, 177.2.

**Data for 32:** yield 0.10 g, 80%; $[\alpha]_D^{25} = +41.7$ ($c = 1.0$, $CHCl_3$); (lit.[27] $[\alpha]_D^{25} = +40.5$ ($c = 0.6$, $CHCl_3$)); IR (KBr) $\upsilon$ 3448, 1712 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 0.93 and 0.95 (d, $J = 6.6$ Hz, 3H), 1.79−1.66 (octet, $J = 6.6$, 1H), 2.45 (dd, $J = 9.9$ Hz, $J' = 16.2$ Hz, 1H), 2.55 (dd, $J = 3.3$ Hz, $J' = 16.2$ Hz, 1H), 3.83 (dt, $J = 12.3$ Hz, $J' = 6.6$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$, $\delta$) 17.6, 18.2, 33.1, 38.3, 68.7, 177.7.

**Data for 33:** yield 0.11 g, 75%; $[\alpha]_D^{25} = +53.0$ ($c = 1.0$, $CHCl_3$); (lit.[28] $[\alpha]_D^{25} = +53.2$ ($c = 1.0$, $CHCl_3$)); IR (KBr) $\upsilon$ 3458, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, $\delta$) 0.93 (s, 9H), 2.41 (dd, $J = 10.3$ Hz, $J' = 16.2$ Hz, 1H), 2.60 (dd, $J = 2.4$ Hz, $J' = 16.2$ Hz, 1H), 3.74 (dd, $J = 2.4$ Hz, $J' = 8.0$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$, $\delta$) 25.6, 34.5, 35.6, 75.6, 178.5.

**General Procedure for the Preparation of Compounds 34−36.** Imidazole (0.17 g, 2.5 mmol) and *tert*-butyldimethylsilyl chloride (0.23 g, 1.5 mmol) were successively added to a solution of compound (**5l**) (0.28 g, 1 mmol) in dry DMF (1.5 mL), and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. Then additional imidazole (0.17 g, 2.5 mmol) and *tert*-butyldimethylsilyl chloride (0.23 g, 1.5 mmol) were added, and the mixture was stirred for 72 h at room temperature. Finally the reaction mixture was poured into water (10−15 mL) at 0 °C and was extracted twice with $Et_2O$. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure to afford a colorless oil. The resulting crude was purified by column chromatography (eluant EtOAc−hexane 1:20) and used in next reaction. Yield: 0.34 g, 86%.

Cerium chloride heptahydrate (1.83 g, 5.0 mmol) was finely powdered in a mortar and then placed into a 25-mL two-necked flask. Most of the water of crystallization was removed in vacuo by immersing the flask in an oil bath heated at 135−140 °C for 2 h. A magnetic stir bar was then inserted, and the cerium chloride was completely dried in vacuo with stirring at the

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same temperature for 1 h. While the flask was still hot, nitrogen gas was introduced and the flask was cooled in an ice bath. Dry THF (8 mL) was then added with stirring, and the resulting suspension was efficiently stirred for 2 h at room temperature. The flask was again immersed in an ice bath, and the Grignard reagent (1.67 ml, 5.0 mmol, 3 M in $Et_2O$) was added. After 1.5 h of stirring at 0 °C, a solution of the corresponding *β*-*tert*-butyldimethylsilyloxy ketone (0.40 g, 1 mmol) in THF (3 ml), obtained as mentioned before, was added, and the resulting mixture was stirred for 2 h at the same temperature. The reaction mixture was treated with water (5 mL) containing acetic acid (0.2 mL) and then extracted with ether. The combined extracts were washed with brine, aqueous $NaHCO_3$ solution, and brine and then dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford compounds **34**−**36** as colorless oils in 80−85% yield.

**Data for 34:** yield 0.35 g, 85%, colorless oil; $^1$H NMR ($CDCl_3$, *δ*) 0.11 and 0.13 (s, 3H), 0.80 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 0.94 and 1.08 (s, 3H), 1.30 (s, 3H), 2.04−1.12 (m, 9H), 2.05 and 2.87 ($s_b$, 1H), 3.71−3.66 (dd, $J$ = 1.8 Hz, $J'$ = 7.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$ *δ*), −2.9, −2.7, 12.9, 19.0, 20.8, 21.9, 23.3, 26.6, 26.7, 29.3, 29.8, 36.4, 40.8, 44.6, 51.3, 53.1, 78.0, 78.5, 85.0.

**Data for 35:** yield 0.40 g, 85%, colorless oil; $^1$H NMR ($CDCl_3$, *δ*) −0.14 (s, 3H), 0.01 and 0.09 (s, 3H), 0.71 (s, 3H), 0.81 (s, 9H), 0.95 (s, 9H), 1.03 (s, 3H), 1.58−1.10 (m, 3H), 1.97−1.72 (m, 4H), 2.23 (d, $J$ = 12.9 Hz, 1H), 2.49 (m, 1H), 2.86 (d, $J$ = 15.3 Hz, 1H), 3.23 (d, $J$ = 8.8 Hz, 1H), 3.76 (s, 1H), 7.59−7.20 (m, 3H), 7.95 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$ *δ*), −2.7, −1.5, 10.8, 19.1, 20.6, 21.9, 26.7, 26.9, 27.0, 28.4, 36.2, 39.6, 41.3, 44.8, 51.2, 53.7, 79.7, 81.1, 85.6, 127.0, 127.1, 128.6, 143.8.

**Data for 36:** yield 0.35 g, 80%, colorless oil; $^1$H NMR ($CDCl_3$, *δ*) 0.15 and 0.17 (s, 3H), 0.79 (s, 3H), 0.88 (s, 8H), 0.91 (s, 9H), 0.97 and 1.03 (s, 3H), 1.31−1.10 (m, 3H), 1.74−1.50 (m, 4H), 2.01 and 2.24 (m, 1H), 2.78−2.50 (m, 2H), 3.50 (s, 1H), 3.82 (d, $J$ = 8.0 Hz, 1H), 5.08 (m, 2H), 6.03 (m, 1H); $^{13}$C NMR ($CDCl_3$ *δ*), −2.6, −2.1, 13.2, 19.0, 20.6, 21.6, 26.1, 26.5, 26.8, 28.5, 36.4, 37.0, 41.4, 44.5, 51.2, 53.3, 78.9, 79.2, 86.4, 116.8, 135.7.

**General Procedure for the Oxidation of Diols 34−36.** A solution of the corresponding diol **34**−**36** (1 mmol) in benzene (4 mL) was cooled to 5 °C and lead tetraacetate (0.87 g, 2 mmol) was added to the solution over a period of 5 min. After the addition was complete, the mixture was stirred at the same temperature for 2 h. Then, a saturated aqueous solution of $NaHCO_3$ (5 ml) was added, and the resulting mixture was filtered through a pad of Celite and washed with $CH_2Cl_2$. The organic solution was washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product thus obtained was subjected to column chromatography (eluant EtOAc−hexane 1:50) to collect, as the first compound, the corresponding ketone that was further purified by distillation. In subsequent collected fractions the starting (*R*)-(+)-camphor was recovered essentially pure in 80−90% yield.

**Data for 37:** yield 0.21 g, 80%, bp 70 °C/0.4 Torr; $[\alpha]_D^{25}$ = +30.4 ($c$ = 1.02, $CH_2Cl_2$); IR (film) $\upsilon$ 1723 cm$^{-1}$; $^1$H NMR ($CDCl_3$, *δ*) −0.06 and 0.06 (s, 3H), 0.84 (s, 9H), 0.86 (s, 9H), 2.15 (s, 3H), 2.48 (dd, $J$ = 6.0 Hz, $J'$ = 17.4 Hz, 1H), 2.62 (dd, $J$ = 4.0 Hz, $J'$ = 17.2 Hz, 1H), 3.94 (dd, $J$ = 4.1 Hz, $J'$ = 6.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$ *δ*), −4.8, −4.0, 18.3, 25.9, 26.1, 31.3, 35.5, 48.1, 74.9, 207.5.

**Data for 38:** yield 0.26 g, 80%, bp 135 °C/0.4 Torr; $[\alpha]_D^{25}$ = +37.9 ($c$ = 0.62, $CH_2Cl_2$); IR (film) $\upsilon$ 1690 cm$^{-1}$; $^1$H NMR ($CDCl_3$, *δ*) −0.20 and 0.07 (s, 3H), 0.82 (s, 9H), 0.90 (s, 9H), 3.08 (d, $J$ = 5.6 Hz, 2H), 4.20 (t, $J$ = 5.1 Hz, 1H), 7.61−7.33 (m, 3H), 7.95 (d, $J$ = 7.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$ *δ*), −4.7, −3.9, 18.3, 26.1, 35.8, 42.8, 75.4, 128.1, 128.4, 132.9, 137.5, 199.1.

**Data for 39:** yield 0.23 g, 80%, bp 140 °C/0.4 Torr; $[\alpha]_D^{25}$ = +32.0 ($c$ = 1.06, $CH_2Cl_2$); IR (film) $\upsilon$ 1717 cm$^{-1}$; $^1$H NMR ($CDCl_3$, *δ*) −0.10 and 0.04 (s, 3H), 0.82 (s, 9H), 0.84 (s, 9H), 2.54 (dd, $J$ = 6.1 Hz, $J'$ = 17.4 Hz, 1H), 2.61 (dd, $J$ = 4.0 Hz, $J'$ = 17.4 Hz, 1H), 3.10 (m, 2H), 3.96 (dd, $J$ = 4.0 Hz, $J'$ = 6.0 Hz, 1H); 5.11 and 5.17 (m, 1H), 5.91 (m, 1H); $^{13}$C NMR ($CDCl_3$ *δ*), −4.8, −3.9, 18.3, 25.9, 26.1, 35.6, 46.8, 48.9, 74.7, 118.8, 130.3, 207.2.

**Preparation of Compound 40.** Imidazole (0.17 g, 2.5 mmol) and *tert*-butyldimethylsilyl chloride (0.23 g, 1.5 mmol) were successively added to a solution of compound **20** (0.38 g, 1 mmol) in dry DMF (1.5 mL), and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. Additional imidazole (0.17 g, 2.5 mmol) and *tert*-butyldimethylsilyl chloride (0.23 g, 1.5 mmol) were then added and the mixture was stirred for 5 h at room temperature. Finally, the reaction mixture was poured into water (10−15 mL) at 0 °C and was extracted twice with $Et_2O$. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure to afford a colorless oil. The resulting crude was purified by column chromatography (eluant AcOEt−hexane 1:20) and used in next reaction: yield 0.45 g, 90%, colorless oil; $^1$H ($CDCl_3$, *δ*) −0.02, 0.03, 0.05 and 0.07 (s, 3H), 0.81 (s, 3H), 0.83 (s, 9H) 0.87 (s, 9H), 0.93 (s, 3H), 1.06 (d, $J$ = 6.3 Hz, 3H), 1.10 (s, 3H), 1.41−1.15 and 1.84−1.54 (m, 3H), 2.20 (dd, $J$ = 3.3 Hz, $J'$ = 14.9 Hz, 1H), 2.24 (m, 1H), 3.27 (dd, $J$ = 9.6 Hz, $J'$ = 14.9 Hz, 1H), 3.45 (s, 1H), 3.77 (dq, $J$ = 2.2 Hz, $J'$ = 6.3 Hz, 1H), 4.06 (ddd, $J$ = 2.2 Hz, $J'$ = 1.1 Hz, $J''$ = 9.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$, *δ*) −4.5, −4.2, −4.1, −2.8, 11.1, 18.2, 19.7, 20.5, 20.9, 25.8, 25.9, 26.1, 26.4, 30.2, 41.2, 41.8, 45.2, 50.8, 52.3, 72.3, 75.0, 87.6, 212.1.

**Preparation of Aldehyde 41.** $BH_3$·THF complex (2 ml, 2 mmol, 1 M in THF) was added to a solution of compound **40** (0.50 g, 1 mmol) in dry THF (3 ml) at 0 °C. After 7 h of stirring the reaction mixture at the same temperature, the mixture was quenched with methanol (3 mL) and stirred for 30 min at room temperature. Finally the solvent was removed under reduced pressure to obtain a white solid. The solid residue thus obtained was subjected to oxidation following the general procedure for the oxidation of diol compounds indicated before to obtain **41** in 70% yield (0.25 g): colorless oil; bp 150 °C/0.5 Torr; $[\alpha]_D^{25}$ = +16.0 ($c$ = 5.0, $CH_2Cl_2$); IR (film) $\upsilon$ 1713 cm$^{-1}$; $^1$H NMR ($CDCl_3$, *δ*) 0.04 (s, 9H), 0.05 (s, 3H), 0.85 (s, 18H), 1.1 (d, $J$ = 6.2 Hz, 1H), 2.46 (ddd, $J$ = 2.0 Hz, $J'$ = 5.3 Hz, $J''$ = 16.0 Hz, 1H), 2.58 (ddd, $J$ = 2.9 Hz, $J'$ = 5.1 Hz, $J''$ = 16.0 Hz, 1H), 3.75 (dq, $J$ = 6.2 Hz, $J'$ = 4.5 Hz, 1H), 3.92 (d, $J$ = 5.1 Hz, 1H), 9.81 (dd, $J$ = 2.1 Hz, $J'$ = 2.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$, *δ*), −4.6, −4.5, −4.2, 18.1, 20.4, 25.9, 47.2, 72.3, 73.4, 202.0.

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**Supporting Information Available:** Characterization data for compounds **5b**−**k**, **10b**,**c**, and **17**, ORTEP diagrams of **3**, **5l**, **20**, and **26**, including X-ray crystallographic data, and copies of $^1$H and $^{13}$C NMR spectra of some representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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