# Chiral Synthesis via Organoboranes. 47. Efficient Synthesis of Unsymmetrical Ketones and Enantiomerically Pure Spiroketals Using (±)-Isopinocampheyldichloroborane

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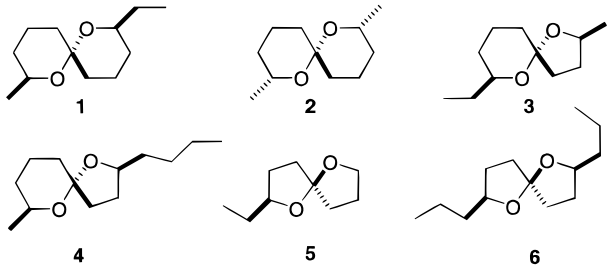
Readily prepared and stable (±)-isopinocampheyldichloroborane [(±)-IpcBCl$_2$] was conveniently used for the stepwise hydroboration of two different alkenes using the in situ reduction−hydroboration protocol to give mixed trialkylboranes, IpcBR$^1$R$^2$. Convenient elimination of α-pinene from these trialkylboranes by treatment with an aldehyde, RCHO, provided the borinate ester, R$^1$R$^2$BOCH$_2$R. This intermediate was readily converted into the unsymmetrical ketones, R$^1$COR$^2$, in high yields and purity, by an established method. This methodology was successfully applied to the synthesis of enantiomerically pure spiroketals using optically pure TBS ether protected homoallylic alcohols as the alkenes for stepwise hydroboration.

Spiroketals occur widely as part of naturally occurring substances from many sources, including insects, microbes, plants, fungi, and marine organisms.[2] The broad spectrum of biological activities possessed by compounds containing spiroketal assemblies has generated great interest in their synthesis and reactivity in recent years.[3] One group of compounds which contains the spiroketal skeleton belongs to the important class of insect pheromones. Many of them contain either a spiro[5.5], -[5.4], or -[4.4] ring system and have unbranched carbon chains on the carbon atom adjacent to the ring oxygen (**1**−**6**, Chart 1).[4]

A number of synthetic strategies have been developed for the synthesis of such enantiomerically pure spiroketals. Among the more common ones are the 1,3-dithiane riveting approach,[3a,h,5] addition of optically pure nucleophiles to optically pure lactones,[6] alkylation of cyclic vinyl ethers,[3g,i,7] and enolate−carbonyl (aldol) condensations.[3d,f,8]

**Chart 1**




However, many of these approaches involve a large number of steps in which the intermediates are often obtained in low enantiomeric purities leading to a complicated mixture of products at the end. In this paper, we report the development of an efficient stepwise hydroboration methodology based on the use of readily prepared and stable (±)-IpcBCl$_2$ for the synthesis of unsymmetrical ketones and enantiomerically pure spiroketals.

## Results and Discussion

During the past decade we have developed several terpene-derived asymmetric allyl- and crotylborating reagents [Ter$_2$BAll, Ter$_2$BCrt$^Z$, and Ter$_2$BCrt$^E$, Ter = $^d$Ipc

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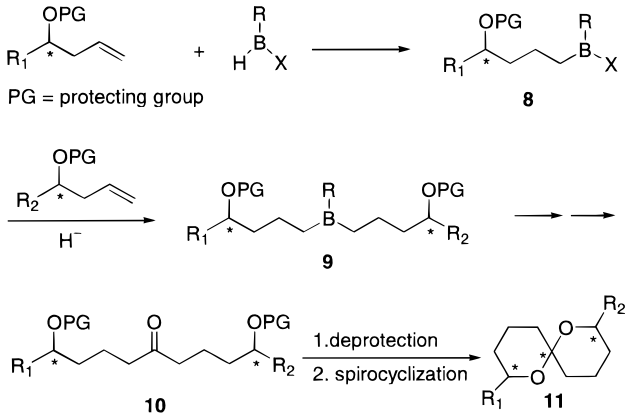
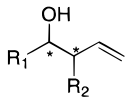
**Scheme 1**




(isopinocampheyl); $^{l}$Ipc, 4-$^{d}$Icr (derived from (+)-3-carene), and 2-$^{d}$Icr (derived from (+)-2-carene)] which can achieve the synthesis of a wide variety of homoallylic alcohols **7**



**7** $R_1$ = alkyl, aryl, alkenyl
$R_2$ = H, Me, etc.

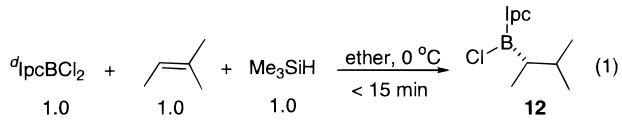
with enantio- and diastereoselectivities approaching 100%.[9] Therefore, we envisaged a synthetic plan which takes advantage of the ready availability of these alcohols to develop a simple methodology for the synthesis of spiroketals in high optical purity.

Our basic approach is outlined in Scheme 1. Stepwise hydroboration of two different protected homoallylic alcohols using a suitable stepwise hydroborating agent would give a trialkylborane intermediate **9** which could be converted into ketone **10** using one of the known methods.[10] Deprotection of the two hydroxyl moieties would lead to a dihydroxy ketone which cyclizes spontaneously into spiroketals **11**. Therefore, we expected that by starting with the correct configurations of the homoallylic alcohols and carrying out the deprotection under acidic conditions, the spiroketal would be formed under thermodynamic control with the same configuration at the spiro carbon as that present in the natural product.

The first objective was to select a protecting group for the homoallylic alcohols which would not interfere with the hydroboration, as well as be stable to the reaction conditions of the subsequent steps. Moreover, it should be possible to remove it, in the last step, under the mild acidic conditions necessary for the equilibration of the spiroketal. We first decided to investigate *tert*-butyldimethylsilyl (TBS) ether as the protecting group since it can be readily removed quantitatively under mild acidic conditions (aqueous HF in $CH_3CN$).[12]

Our next goal was to find a suitable stepwise hydroborating agent which would permit the clean stepwise hydroboration of two different TBS-protected homoallylic alcohols without cleavage of the protecting groups, giving high yields of the corresponding ketones with minimum scrambling.[13] The dibromoborane reagent $BHBr_2{\cdot}SMe_2$ has been reported[14] as such a stepwise hydroborating agent for the preparation of unsymmetrical ketones from two different terminal alkenes. However, the harsh nature of this reagent made it unsuitable for the present case. Thexylchloroborane (in which thexyl group serves as the anchor group) has been used in some cases for stepwise hydroboration of functionalized alkenes.[15] However, it too suffers from certain disadvantages in the present application. For example, one of the ways to convert the *B*-thexyl group into the carbonyl group requires carbonylation under high pressures and temperatures.[10a] Another way to achieve this conversion is to use the cyanidation reaction,[10d] which requires rigorously dry cyanide and fails to proceed in the presence of Li or Mg salts.[10b] Similarly, triisopropylphenylborane ($TripBH_2$)[16] suffers from the disadvantage that multiple steps are required for its preparation.

During the past several years, we have developed several valuable reagents based on α-pinene as the chiral auxiliary.[17] Some of these reagents include $Ipc_2BH$, $IpcBH_2$, $Ipc_2BAll$, and $Ipc_2BCl$ (Ipc = isopinocampheyl). Recently, we have demonstrated the remarkable effect of an ether solvent in the reduction of $IpcBCl_2$ with $Me_3SiH$ (1 equiv each).[18] For example, the reaction of equivalent amounts of $IpcBCl_2$ with $Me_3SiH$ in the presence of 2-methyl-2-butene (1 equiv) at 0 °C was complete in only 15 min in ether to give clean dialkylchloroborane **12** (eq 1), while the same reaction carried




out in pentane required almost 2 days for completion.[18] This result contrasts strongly with the hydroboration characteristics of the thexylchloroborane−dimethyl sulfide complex ($ThxBHCl{\cdot}SMe_2$), which requires 1 h at 25 °C even with monosubstituted terminal olefins.[19]

On the basis of these observations, we decided to investigate the possibility of using (±)-$IpcBCl_2$ for the stepwise hydroboration in this study.[20] It was expected that the second hydroboration would be achieved by

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(16) Smith, K.; Pelter, A. Jin, Z. *J. Chem. Soc., Perkin Trans. 1* **1993**, 395.

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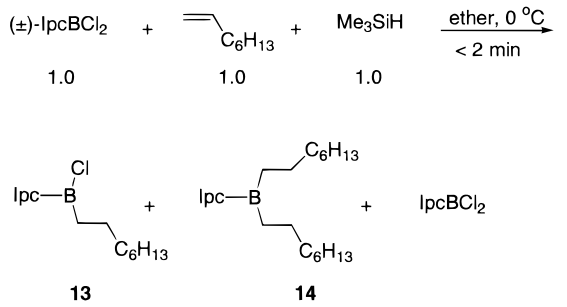
(18) Dhokte, U. P.; Kulkarni, S. V.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 5140.

(19) Brown, H. C.; Sikorski, J. A.; Kulkarni, S. U.; Lee, H. D. *J. Org. Chem.* **1982**, *47*, 863.

hydridation of the dialkylchloroborane (formed in the first step) in the presence of the second olefin.[21] Moreover, on the basis of our previous studies, it was expected that, after the stepwise hydroboration of two different alkenes, the trialkylborane could be readily and quantitatively converted into a borinate by elimination of α-pinene by treatment with an aldehyde.[22] The dialkylborinates could then be converted into the corresponding unsymmetrical ketones via the DCME reaction, which generally proceeds in high yield and is not very susceptible to reaction conditions.[10c]

(±)-IpcBCl$_2$ ($\delta$ 62, $^{11}$B NMR) was conveniently prepared in essentially quantitative yield in one step from (α-pinene and $BCl_3$ using $Me_3SiH$.[23] It showed no detectable change in $^1$H and $^{13}$C NMR, even at room temperature when stored under nitrogen for 4 months.

To test the feasibility of this approach and to standardize the reaction conditions, we decided to try the reactions first with the simple terminal alkenes 1-octene and 1-hexene. As expected, the in situ reduction−hydroboration reaction of (±)-IpcBCl$_2$ with 1.0 equiv of $Me_3SiH$ in ether in the presence of 1 equiv of 1-octene was quite fast, complete in less than 2 min at 0 °C. However, the required dialkylchloroborane **13** ($\delta$ 76, $^{11}$B NMR) was contaminated with about 5% each of the trialkylborane **14** ($\delta$ 83, $^{11}$B NMR) and (±)-IpcBCl$_2$ (eq 2).

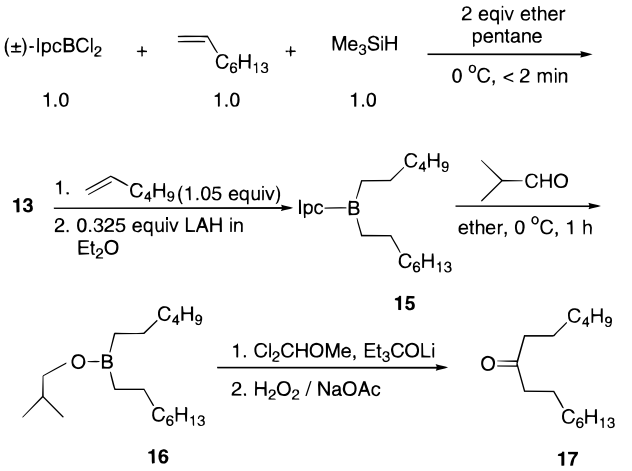



(2)

Gratifyingly, when the same reaction was carried out in pentane with 2 equiv of ether, the hydroboration was equally as fast and the $^{11}$B NMR showed dialkylchloroborane **13** free from any other boron species (Scheme 2). Remarkably, even when 2 equiv of $Me_3SiH$ was used, equally clean hydroboration was observed.[24]

Having successfully solved the first hydroboration step, we next tackled the second hydroboration. $Me_3SiH$ was not successful in achieving the hydridation required for the second hydroboration even in ethyl ether as the solvent. Such hydridations are generally carried out using either $LiAlH_4$ (LAH) or potassium triisopropoxyborohydride (KIPBH).[21] Considering the ready availability of LAH, we decided to use it for the hydridation step. The hydridation is almost always carried out in

**Scheme 2**




the presence of the second alkene to minimize the amount of scrambling, which otherwise ultimately leads to significant contamination of the required unsymmetrical ketone by the symmetrical ketone.[21] We investigated this hydridation step in the presence of a slight excess (1.05 equiv) of 1-hexene at various temperatures (−25 °C, 0 °C, room temperature) and in different solvents (ether, pentane, ether−pentane) to find conditions which would provide a minimum of scrambling.[25] From this study it was found that simply adding 1.3 times the theoretical amount (i.e. 1.3 × 0.25 equiv) of LAH (as a 1.0 M solution in ether) to the reaction mixture of the first hydroboration step in the presence of 1.05 equiv of 1-hexene at 0 °C gave the clean trialkylborane **15**.

The reason for adding 1.3 times the theoretical amount of LAH is the fact that $Me_3SiCl$ formed in the first step also reacts with LAH but at much slower rate than that of the dialkylchloroborane. Thus, not removing the $Me_3SiCl$ from the reaction mixture prior to the hydridation step has two advantages: (i) It simplifies the experimental procedure since the time required for its evaporation from the reaction mixture is saved, and (ii) it reacts with any excess LAH added, preventing the decomposition of required trialkylborane to dialkylboranes and borohydrides. After the hydridation step, the residual $Me_3SiCl$ (bp 57 °C), $Me_3SiH$ (bp 7 °C), and solvents were readily removed to give trialkylborane **15** along with a white precipitate of $AlCl_3$ and LiCl (Scheme 2).

The elimination of α-pinene from trialkylboranes of the type **15** to give dialkylborinates **16** has earlier been studied with various aldehydes.[26] For the present study, we chose isobutyraldehyde since (i) it reacts faster than other aldehydes such as acetaldehyde, (ii) it would ultimately lead to isobutanol which could be readily separated from the products either by distillation or by washing with water, and (iii) it provided a slightly more hindered borinate as compared to that with acetaldehyde or benzaldehyde. It is known that, for a borinate having less hindered alkyl groups, the yield achieved in the DCME reaction increases with increase in the steric bulk of the alkoxy group.[10c] The elimination of α-pinene with

(20) The much faster rate of hydroboration using this method as compared to thexylchloroborane was thought to be advantageous since the protected homoallylic alcohol would remain in contact with the chloroborane for a much shorter time and at a lower temperature, which should minimize side reactions.

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(22) Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, S. *Organometallics* **1986**, *5*, 2138.

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(24) Since an excess of $Me_3SiH$ was not found to have any deleterious effect on the reaction, a moderate excess (1.5 equiv) of it was used to avoid having to measure accurately this low-boiling (bp 7 °C) liquid.

(25) To find the amount of scrambling, the trialkylborane **15** in each case was converted into the unsymmetrical ketone **17**, as described in this paper. The amounts of di-*n*-hexyl ketone and di-*n*-octyl ketone formed along with this unsymmetrical ketone **17** gave a direct measure of the amount of scrambling.

(26) Joshi, N. N.; Pyun, C.; Mahindroo, V. K.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 504.

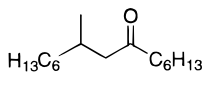
**Table 1. Synthesis of Unsymmetrical Ketones by Stepwise Hydroboration Using (±)-IpcBCl$_2$**

| alkene 1 | alkene 2 | product[a] | % yield |
|---|---|---|---|
| 1-octene | 1-hexene | **17** | 93[b] |
| 2-methyl-1-octene | 1-hexene | **18** | 85[b] |
| 1-hexene | 4-vinyl-1-cyclohexene | **19** | 82[b] |
| **20** | 1-hexene | **23** | 81[c] |
| **26** | 1-hexene | **27** | 79[c] |

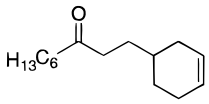
[a] ≤5% symmetrical ketones were also formed in the reaction. [b] GC yield. [c] Yield of pure isolated compound.

isobutyraldehyde was somewhat slow in pentane, but in ether it was complete in 1 h at 0 °C, giving cleanly the required **16**. The dialkylborinate **16** ($\delta$ 53, $^{11}$B NMR) was then subjected to the DCME reaction after replacing ether with THF. The intermediate α-chloroboronate obtained upon alkaline peroxide oxidation provided a 93% yield (by GC) of the required unsymmetrical ketone **17**. The amount of scrambling represented by the amounts of symmetrical ketones formed, viz. dihexyl and dioctyl ketones, was less than 5% (Scheme 2).

Thus we had achieved an efficient and convenient synthesis of the unsymmetrical ketone **17**. The remarkable features of this synthesis were that both the hydroboration steps were complete in less than 30 min, even at 0 °C, and the whole sequence of reactions was carried out successfully in one pot for the synthesis of two more simple ketones **18** and **19** (Table 1).

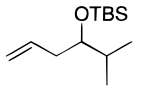



**18**

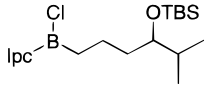



**19**

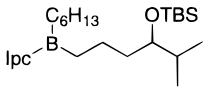
The real test now was whether these conditions would hold true for the stepwise hydroboration of protected homoallylic alcohols, as needed for the spiroketal synthesis. Since we expected that if there was going to be any problem in the sequence, it would be in the first step, we decided to use 1-hexene as the second alkene until we had established the proper choice of the protecting group. To test the feasibility of a TBS ether protecting group, the racemic homoallylic TBS ether **20** was subjected to the first hydroboration conditions established earlier. The required dialkylchloroborane **21** was formed cleanly in less than 10 min at 0 °C and showed a peak at $\delta$ 76 indicating that there was no complexation between the oxygen and the boron atom of **21**. The second hydroboration in the presence of a slight excess of 1-hexene with LAH under previously described conditions also proceeded cleanly to give trialkylborane **22**. In both of the hydroboration steps there was no indication of any decomposition or formation of other boron species. The trialkylborane **22** was then converted into the corresponding unsymmetrical ketone **23** in 81% yield without any incident (Table 1).



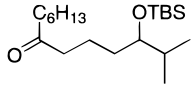

**20**




**21**



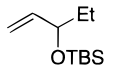

**22**



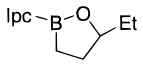

**23**

Thus, TBS ethers were good protecting groups for the homoallylic alcohols. It became clear that this method can now be used for the synthesis of [5.5] spiroketals as we had hoped to achieve. It occurred to us that if we could establish that the TBS ether works well for allylic alcohols as well, then this method could be extended to the synthesis of optically pure [4.4] and [4.5] spiroketals, since a number of methods are also available for the preparation of allylic alcohols in high optical purity.[27]

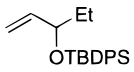
For this purpose, a TBS-protected racemic alcohol **24** was subjected to the same reaction conditions established earlier. To our surprise, although the first hydroboration took place as readily as before, the product dialkylchloroborane was not stable and had undergone considerable cleavage of the TBS group, as evidenced by the presence of a borinate ($\delta$ 53) in the $^{11}$B NMR taken after 10 min at 0 °C. The amount of borinate (most likely **25**) gradually increased as the reaction mixture was kept at 0 °C. Fortunately, when the protecting group was changed to a *tert*-butyldiphenylsilyl ether (TBDPS, **26**), no trace of cleavage was observed in either of the two hydroboration steps and the corresponding unsymmetrical ketone **27** was obtained in 79% yield (Table 1).



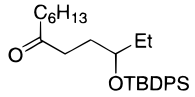

**24**




**25**

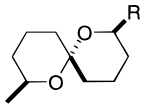



**26**




**27**

After establishing proper protecting groups for the homoallylic and allylic alcohols, we were ready to demonstrate the application of this methodology for the synthesis of enantiomerically pure spiroketals. We selected first a symmetrical substituted [5.5] spiroketal **28**,




**28**: R = Me
**29**: R = Pr

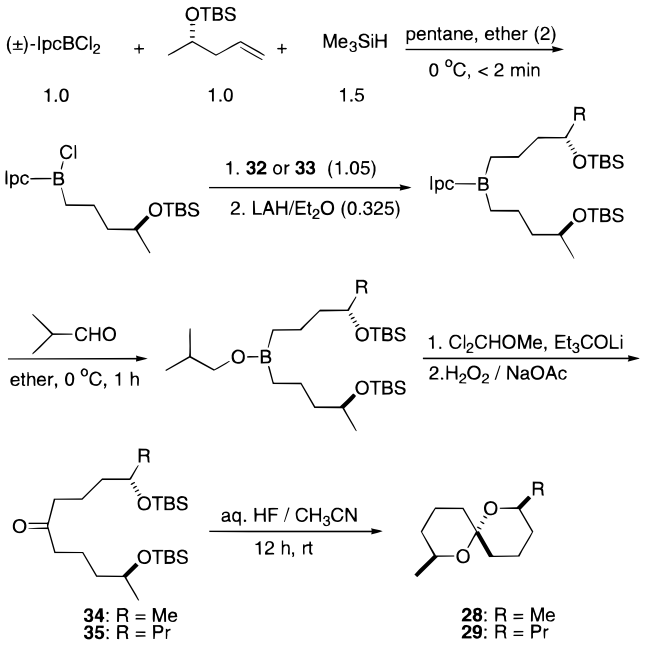
a major glandular component of the cucumber fly *Dacus cucumis*[28] as the target molecule. It exists exclusively in a conformation in which both C−O bonds are axial to the other ring and the two methyl groups are in a equatorial arrangement. The synthesis of **28** has been reported in the literature by various groups.[29]

(27) (a) Sugimoto, K.; Aoyagi, S.; Kabayashi, C. *J. Org. Chem.* **1997**, *62*, 2322. (b) Dorta, R. L.; Rodriguez, M. S.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1997**, *38*, 4675. (c) Keck, G. *J. Am. Chem. Soc.* **1993**, *115*, 8467 and references therein.

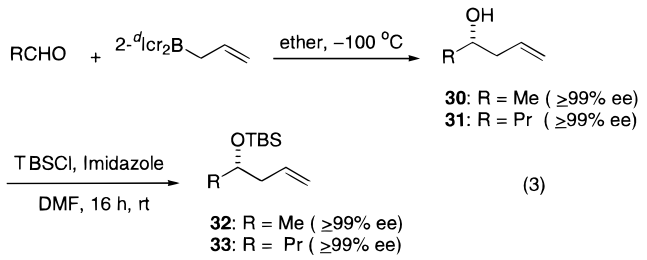
(28) Kitching, W.; Lewis, J. A.; Perkins, R. A.; Drew, R. A.; Moore, C. J.; Francke, W.; Konig, W. A.; Schurig, V. *J. Org. Chem.* **1989**, *54*, 3893.

(29) (a) Solladie, G.; Huser, N. *Tetrahedron: Asymmetry* **1994**, *5*, 255. (b) Mori, K.; Tanida, K. *Tetrahedron* **1981**, *37*, 3221. (c) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295. (d) Perkins, M. V.; Kitching, W.; Konig, W. A.; Drew, R. A. I. *J. Chem. Soc.. Perkin Trans. 1* **1990**, 2501. (e) Yadav, J. S.; Gadgil, V. R. *Tetrahedron Lett.* **1990**, *31*, 6217.

**Scheme 3**




The homoallylic alcohol **30** (R = Me) required for the synthesis of **28** was prepared in ≥99% ee using our well-established allylboration methodology (eq 3).[9] It was




then protected as the TBS ether derivative **32** and converted into ketone **34** (R = Me) in 79% yield using stepwise hydroboration (Scheme 3). Deprotection of the two TBS groups of **34** with aqueous HF in $CH_3CN$ provided only the required diastereoisomer of **28**. Further analysis of **28** by capillary GC and $^1H$ and $^{13}C$ NMR revealed the formation of the desired diastereoisomer **28** in the reaction. Comparison of the specific rotation with the literature value[29] indicated that the spiroketal **28** was of ≥99% ee, confirming that no racemization had taken place under the reaction conditions.[30]

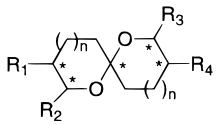
To test this methodology for unsymmetrically substituted spiroketal synthesis, we decided to synthesize spiroketal **29**. This is one of the many spiroketals present in the mandibular gland secretion of female *Andrena haemorrhoa*.[4c] It occurs in nature as a single diastereoisomer having both the C−O bonds in an axial orientation and the alkyl groups in equatorial positions. Even though this relative configuration was known, the specific rotation and absolute configuration i.e., whether it is (2*R*,6*S*,8*R*) or (2*S*,6*R*,8*S*) was not known. We arbitrarily decided to synthesize the latter isomer since this method should be readily applicable to the synthesis of either isomer with proper choice of the enantiomerically pure homoallylic alcohols.

The required homoallylic alcohols (R = Me, **30**, and Pr, **31**) were prepared via asymmetric allylboration in ≥99% ee.[9] Application of the stepwise hydroboration protocol using (±)-$IpcBCl_2$ as shown in Scheme 3 provided, after DCME reaction and hydrogen peroxide oxidation, the unsymmetrical ketone **35** (R = Pr) in 75% yield along with about 5% of the symmetrical ketones. Pure ketone **35** was readily obtained by column chromatography, which on treatment with aqueous HF in $CH_3CN$ provided, as expected, spiroketal **29** as a single diastereomer in ≥99% ee.[30] Taking into account the anomeric effect[11] and the known absolute configurations of the starting homoallylic alcohols, the product is the undoubtedly the required (2*S*,6*R*,8*S*) isomer.

## Conclusions

A new and stepwise hydroboration methodology based on the use of (±)-$IpcBCl_2$ has been developed for the synthesis of unsymmetrical ketones and enantiomerically pure spiroketals. Notable features of this methodology are the following: (i) (±)-$IpcBCl_2$ can be prepared in one step from inexpensive (±)-α-pinene and is stable at room temperature for extended periods of time when stored under a nitrogen atmosphere. (ii) Both the hydridation steps can be completed in less than 30 min at 0 °C, and a little excess of the hydride reagent does not adversely affect the reaction. (iii) All the steps can be carried out in one-pot in a matter of 10−12 h, and the unsymmetrical ketones are obtained in high yields and purity. We believe that this methodology can be extended to the synthesis of more highly substituted optically active spiroketals **37** by making use of the ready availability of variously substituted homoallylic alcohols **7** and allylic alcohols **36** in high enantiomeric excess.


**36**: R = alkyl, aryl, alkenyl




**37**: $R_1$, $R_2$ = alkyl, aryl, alkenyl
n = 1, $R_1$, $R_4$ = H, Me, OR
n = 0; $R_1$, $R_4$ = H

## Experimental Section

All reaction flasks and equipment were dried at 150 °C for several hours prior to use and assembled hot under a stream of nitrogen. Special techniques for handling air-sensitive materials are described elsewhere.[31] Boiling points reported are uncorrected. All $^1H$ NMR were recorded at 300 MHz, while all $^{13}C$ NMR were recorded at 50.1 MHz in $CDCl_3$ with TMS as internal standard. Chemical shifts in the $^1H$ and $^{13}C$ NMR spectra are reported as parts per million (ppm) downfield from TMS. Flash chromatography was performed on silica gel (230−400 mesh, Merck). Preparative gas chromatography was performed on a 6 ft × 0.25 in. column packed with 10% SE-30 on chromosorb W (100−120 mesh, AW DMCS). Specific rotations [α] were determined at the sodium D line at 25 °C.

(30) We expect it to be of ≥99% ee since the starting homoallylic alcohols were of ≥99% ee and it was established in the preparation of **28** that no racemization takes place under the reaction conditions. This is confirmed by the absence of other diastereomers of **28** in the $^1H$ and $^{13}C$ NMR since any racemization would have resulted in the formation of diastereomers of **28**. Further, the enantiomeric purity of the spiroketal **29** was confirmed by chiral capillary GC in comparison with the racemic spiroketal.

(31) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975. A reprinted edition of Vol. 1, Aldrich Chemical Co., Inc., Milwaukee, WI, 1997, is currently available.

Unless otherwise mentioned, the reagents and starting materials were purchased from commercial sources and used directly. Pentane was stored over 4-Å molecular sieves and used directly in all experiments. THF was dried by distillation over sodium−benzophenone ketyl. Enantiomerically pure homoallylic alcohols **30** and **31** (R = Me, Pr) were prepared according to the literature procedure in >99% ee using 2-$^{d}$Icr$_2$-BAllyl.[9] Silyl ethers **20**[32] and **30**[33] (R = Me) were also prepared using literature procedures.

**(±)-Isopinocampheyldichloroborane [(±)-IpcBCl$_2$].** To the cold (−78 °C) solution of $BCl_3$ (1.0 M, 10 mmol) in pentane, a cold (−78 °C) mixture of precondensed $Me_3SiH$ (10 mmol) and (±)-α-pinene (10 mmol) was added slowly. The reaction mixture was stirred for 10 min at that temperature and then allowed to warm to ambient temperature. The $^{11}$B NMR showed complete formation of (±)-IpcBCl$_2$ (singlet at δ 64). The volatiles of the reaction mixture were removed (15 mmHg, room temperature, 0.5 h), and residual liquid was purified by distillation under reduced pressure: bp 60−5 °C (0.2 mmHg); $^1$H NMR δ 1.80−2.40 (m, 6H), 1.20 (s, 3H), 1.12 (d, *I* = 7.2 Hz, 3H), 1.06 (s, 3H), 0.86 (d, *J* = 9.6 Hz, 1H); $^{13}$C NMR 47.63, 40.87, 38.61, 33.13, 29.64, 28.15, 22.89, 22.64.

**3-((*tert*-Butyldiphenylsilyl)oxy)-1-pentene (26).** To a solution of *tert*-butyldiphenylsilyl chloride (7.56 g, 27.5 mmol), imidazole (3.88 g, 57.0 mmol), and DMAP (0.06 g, 0.5 mmol) in DMF (13.5 mL) was added 1-penten-3-ol (2.15 g, 25.0 mmol), and the reaction mixture was stirred at room temperature for 16 h. It was worked up by adding hexane (50 mL) followed by washing with 1 N HCl (2 × 25 mL), and water (25 mL). The organic layer was concentrated and fractionated under reduced pressure to give **26** (7.45 g, 92%) in >95% purity. A small sample was purified by flash chromatography (98:2 hexane/ethyl acetate): colorless oil; $^1$H NMR δ 7.61−7.75 (m, 4H), 7.30−7.46 (m, 6H), 5.71−5.84 (m, 1H), 4.92−5.04 (m, 2H), 4.06−4.15 (m, 1H), 1.40−1.60 (m, 2H), 1.07 (s, 9H), 0.77 (t, 3H); $^{13}$C NMR δ 140.53, 135.96, 135.88, 134.57, 134.33, 129.47, 129.40, 127.41, 127.31, 114.34, 75.66, 30.28, 27.04, 19.38, 8.74.

**(4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-heptene (33, R = Pr).** Prepared from 1-hepten-4-ol by a procedure similar to that of **26** using TBSCl instead of TBDPSCl: colorless oil, bp 110−5 °C (26 mmHg); $^1$H NMR δ 5.70−5.90 (m, 2H), 4.97−5.09 (m, 2H), 3.63−3.73 (m, 1H), 2.15−2.24 (m, 2H), 1.20−1.47 (m, 4H), 0.85−0.93 (m, 12H), 0.05 (s, 6H); $^{13}$C NMR δ 135.51, 116.51, 71.82, 42.01, 39.13, 25.91, 18.61, 18.61, 18.16, 14.26, −4.37, −4.54.

**General Procedure for the Preparation of Unsymmetrical Ketones 17−19, 23, and 27.** The procedure described for the preparation of 3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-7-tridecanone (**23**) is representative.

To a stirred solution of (±)-IpcBCl$_2$ (2.19 g, 10.0 mmol) in pentane (8.0 mL) and ether (2.09 mL, 20.0 mmol) at 0 °C was added alkene **20** (2.19 g, 10.0 mmol). To this solution was immediately added precooled (−78 °C) $Me_3SiH$ (1.11 g, 15.0 mmol) via a double-ended needle and stirred for 10 min. 1-Hexene (0.88 g, 10.5 mmol) was added, followed by a dropwise addition of LAH (1.0 M solution in ether, 3.25 mL, 3.25 mmol). The ice bath was removed after 4 min, and the reaction mixture was brought to room temperature (30 min). Solvents and other volatiles were removed under reduced pressure (12 mmHg, 30 min), and the residue was diluted with ether (10.0 mL) and cooled to 0 °C. Isobutyraldehyde (0.86 g, 12.0 mmol) was added, and the reaction mixture was stirred for 1 h. Ether and excess aldehyde were removed under reduced pressure (12 mmHg, room temperature), and the residue was dissolved in THF (10.0 mL) and cooled to −10 °C. To this solution was added α,α-dichloromethyl methyl ether (2.87 g, 25 mmol) followed by a dropwise addition of $Et_3COLi$ (25.0 mmol, prepared by reaction of $Et_3COH$ and BuLi) over 10 min. The reaction mixture stirred for 30 min then warmed to room temperature (LiCl precipitated out), and it was further stirred for 2 h. The reaction mixture was then concentrated to half the volume and diluted with EtOH (5.0 mL). It was then subjected to oxidation by adding 3 M NaOAc (10.0 mL, 30% $H_2O_2$, 4.5 mL, 40.0 mmol), and heating was continued at 70 °C for 2 h with vigorous stirring.

The reaction mixture was then diluted with ether (40.0 mL), and the aqueous layer was discarded. The organic layer was washed with water (2 × 25 mL), dried over anhydrous $MgSO_4$, and concentrated. After removal of $Et_3COH$ and other low-boiling impurities from the reaction mixture by heating at 100 °C in an oil bath (12 mmHg), the product was distilled at 0.2 mmHg in a Kugelrohr apparatus to provide crude ketone **23** in approximately 90% purity. It was further purified by flash chromatography (98:2 hexane/ethyl acetate) to give pure **23** as a colorless oil (2.77 g, 81%): $^1$H NMR δ 3.43 (q, *J* = 5.4 Hz, 1H), 2.38 (t, *J* = 7.5 Hz, 4H), 1.44−1.78 (m, 5H), 1.22−1.40 (m, 8H), 0.80−0.92 (m, 18H), 0.033 (s, 3H), −0.028 (s, 3H); $^{13}$C NMR δ 211.40, 76.62, 43.06, 42.06, 42.99, 42.75, 32.64, 31.64, 28.96, 25.95, 23.86, 22.52, 20.00, 18.16, 18.01, 14.04, −4.26, −4.47.

**7-Pentadecanone (17):**[34] $^1$H NMR δ 2.38 (t, *J* = 7.5 Hz, 4H), 1.45−1.61 (m, 4H), 1.27 (bs, 16H), 0.88 (t, *J* = 6.6 Hz, 6H).

**7-Methyl-9-pentadecanone (18):** colorless oil; $^1$H NMR δ 2.32−2.42 (m, 3H), 2.19 (dd, *J* = 8.1, 15.9 Hz, 1H), 1.91−2.07 (m, 1H), 1.50−1.61 (m, 2H), 1.10−1.40 (bs, 16H), 0.83−0.92 (m, 9H); $^{13}$C NMR δ 211.53, 50.36, 43.42, 37.00, 31.87, 31.64, 29.46, 29.27, 28.95, 26.95, 23.79, 22.66, 22.52, 19.91, 14.10, 14.04. Anal. Calcd for $C_{16}H_{32}O$: C, 79.93; H, 13.41. Found: C, 79.99; H, 13.42.

**1-(3-Cyclohexenyl)-3-nonanone (19):** colorless oil; $^1$H NMR δ 5.65 (bs, 2H), 2.36−2.48 (m, 4H), 1.98−2.13 (m, 3H), 1.43−1.78 (m, 7H), 1.15−1.35 (m, 7H), 0.88 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR δ 211.68, 127.04, 126.23, 42.86, 40.33, 33.32, 31.65, 31.63, 30.44, 28.96, 28.71, 25.15, 23.90, 22.51, 14.04. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02, H, 11.78. Found: C, 80.65; H, 11.51.

**3-(*tert*-Butyldiphenylsiloxy)-6-dodecanone (27):** colorless oil; $^1$H NMR δ 7.63−7.70 (m, 4H), 7.32−7.46 (m, 6H), 3.63−3.72 (m, 1H), 2.15−2.45 (m, 4H), 1.55−1.80 (m, 2H), 1.36−1.54 (m, 4H), 1.17−1.37 (m, H), 1.05 (s, 9H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.76 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR δ 211.44, 135.87, 134.54, 134.38, 129.55, 129.51, 127.52, 127.45, 42.75, 38.19, 31.60, 29.30, 29.23, 28.90, 27.07, 23.86, 22.50, 19.42, 14.04, 9.29. Anal. Calcd for $C_{28}H_{42}O_2Si$: C, 76.66, H, 9.65. Found: C, 77.02; H, 9.80.

**(2*R*,6*R*,8*S*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane (28).** Ketone (2*S*,10*S*)-2,10-bis-(*tert*-butyldimethylsiloxy)-6-undecanone (**34**, R = Me) was prepared in 79% yield using the same procedure as described for **27** except that alkene **32** was used in both the hydroboration steps (2.00 g, 10.0 mmol, was used in each step): colorless oil; $[\alpha]_D$ = 13.1° (*c* 1.10, $CHCl_3$); $^1$H NMR δ 3.72−3.84 (m, 2H), 2.39 (t, *J* = 7.2 Hz, 4H), 1.46−1.73 (m, 4H), 1.28−1.45 (m, 4H), 1.12 (d, *J* = 6.0 Hz, 6H), 0.88 (s, 18H), 0.44 (s, 12H); $^{13}$C NMR δ 211.18, 68.37, 42.77, 39.15, 25.90, 23.73, 20.15, 18.13, −4.38, −4.71.

Conversion of ketone **34** (2.37 g, 5.5 mmol) to spiroketal **28** was achieved by simply treating **34** with HF/$CH_3CN$ (33.8 mL of a 5% solution of 48% aqueous HF solution in $CH_3CN$, 44.0 mmol) for 12 h at room temperature. The reaction mixture was then treated with saturated aqueous $K_2CO_3$ (20 mL) and diluted with ether (30 mL). The aqueous layer was discarded, and the organic layer was dried over anhydrous $MgSO_4$. It was then carefully concentrated using a Vigruex column, and the residue was chromatographed using flash column chromatography (1:9 ether/hexane) to give spiroketal **28** (0.52 g, 51%) (the high volatility of **28** is responsible for the low yield): colorless oil. Capillary GC and $^1$H and $^{13}$C NMR analyses of a crude sample established the formation of the desired diastereoisomer. $^1$H NMR: δ 3.62−3.76 (m, 2H), 1.80−1.98 (m, 2H), 1.46−1.63 (m, 6H), 1.31−1.43 (m, 2H), 1.08−1.24 (m, 8H). $^{13}$C NMR: δ 96.17, 65.01, 35.22, 32.81, 21.89, 18.95. The spectral properties agreed very well with those reported in the literature.[29c] $[\alpha]_D$ = −57.6° (*c* 1.04, pentane) (lit.[29c] $[\alpha]_D$ = −56.0° (*c* 1.40, pentane).

(32) Hoffman, R. W.; Bewersdorf, M. *Chem. Ber.* **1991**, *124*, 1259.
(33) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883.

**(2*R*,6*R*,8*S*)-2-Methyl-8-propyl-1,7-dioxaspiro[5.5]-undecane (29).** Ketone (2*S*,10*S*)-2,10-bis(*tert*-butyldimethylsiloxy)-6-tridecanone (**35**, R = Pr) was prepared in 75% yield using the same procedure as described for **27** except that in the first hydroboration alkene **33** (2.00 g, 10.0 mmol) and in the second hydroboration alkene **32** (2.39 g, 10.5 mmol) were used: colorless oil; $[\alpha]_D = 7.3°$ (*c* 1.00, $CHCl_3$); $^1$H NMR $\delta$ 3.76 (sextet, $J = 6.3$ Hz, 1H), 3.64 (pentet, $J = 6.3$ Hz, 1H), 2.38 (t, $J = 7.2$ Hz, 4H), 1.21−1.72 (m, 12H), 1.20 (d, $J = 6.3$ Hz, 3H), 0.84−0.92 (m, 21H), 0.05 (s, 6H), 0.04 (s, 6H); $^{13}$C NMR $\delta$ 211.17, 71.86, 68.37, 42.93, 42.77, 39.32, 39.15, 36.57, 25.93, 23.74, 20.16, 19.72, 18.51, 18.13, 14.32, −4.38, −4.43, −4.71.

Ketone **35** (2.11 g, 4.6 mmol) was stirred for 12 h at room temperature with HF/$CH_3CN$ (28.3 mL of a 5% solution of 48% aqueous HF solution in $CH_3CN$, 36.8 mmol), and the reaction mixture worked up as described for **28** provided pure **29** (0.85 g, 87%) as a colorless oil. The enantiomeric purity (≥99%) of **29** was determined by analyzing it on chiral capillary GC (Chiraldex GTA, 23 m, 65 °C, isothermal) under conditions where the racemic spiroketal **29** (prepared from the corresponding racemic homoallylic alcohols and relevant spiroketal diastereoisomers isolated by preparative GC) had shown an almost 1:1 ratio of the two well-resolved enantiomers. $[\alpha]_D = -78.1°$(*c* 1.71, $CHCl_3$). $^1$H NMR: $\delta$ 3.64−3.77 (m, 1H), 3.49−3.60 (m, 2H), 1.08−1.63 (m, 17H), 0.92 (t, $J = 7.2$ Hz, 3H).). $^{13}$C NMR: $\delta$ 95.96, 68.69, 65.06, 38.77, 35.56, 35.36, 32.88, 31.42, 21.85, 19.15, 19.02, 18.95, 14.26. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.34, H, 11.39. Found: C, 73.31; H, 11.61. The spectral properties agreed well with those reported in the literature[35] for racemic **29**.

**Acknowledgment.** We gratefully acknowledge the financial support of this research by the National Institutes of Health (Grant GM 10937) and the Borane Research Fund.

**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for all new compounds described in the Experimental Section (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980989W

(34) Smith, K.; Pelter, A.; Jin, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 851.

(35) O'Shea, M. G.; Kitching, W. *Tetrahedron* **1989**, *45*, 1177.