Synthesis of Isopropenylcyclopropanes − Revision of the Relative Configuration of Cyclopropyl Ketones Obtained by 1,3-Elimination of γ-Epoxy Ketones

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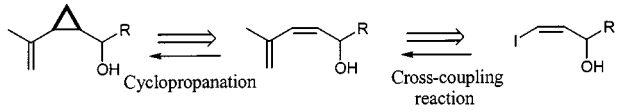
Efficient stereoselective routes towards isopropenylcyclopropanes have been devised. Secondary *cis*-isopropenylcyclopropylcarbinols have been obtained either by regio- and stereoselective hydroxy-directed cyclopropanation of the corresponding dienols or from bicyclic cyclopropyl lactones derived from intramolecular cyclopropanation of allylic diazoacetates. Contrary to previous reports, base-induced 1,3-elimination of γ-epoxy ketones has been shown to afford *trans*-2-(hydroxymethyl)cyclopropyl ketones, and the reactivity of these compounds has been reinvestigated.

Introduction

Cyclopropane-containing organic compounds can undergo a wide variety of ring-opening reactions and are therefore regarded as synthetically useful building blocks for achieving cyclic and acyclic stereocontrol.[1] We have recently reported that electrophilic additions to *cis*-substituted isopropenylcyclopropanes proceed with high levels of stereocontrol,[2,3] therefore providing a complementary strategy to nucleophilic additions to cyclopropyl ketones for the introduction of stereocenters adjacent to the cyclopropane ring.[4] In order to broaden the scope of electrophilic additions to *cis*-substituted isopropenylcyclopropanes, efficient synthetic routes towards these compounds have had to be devised, and we report herein our results concerning the three different routes that have been investigated. With regard to one route, several observations led us to reinvestigate the stereochemical outcome of the base-induced 1,3-elimination of γ-epoxy ketones.

Results and Discussion

According to a first retrosynthetic analysis, we anticipated that *cis*,*syn*-isopropenylcyclopropylcarbinols could be obtained by performing a regio- and stereoselective cyclopropanation of the corresponding dienyl alcohols, which, in turn, should be accessible by standard cross-coupling reactions of two alkenyl moieties (Scheme 1).



Scheme 1. Retrosynthetic analysis for *cis*-isopropenylcyclopropylcarbinols

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Thus, the readily available (*Z*)-γ-iodoallylic alcohols **1a**[5a] and **1b**[5b] were converted into their zinc alkoxides by treatment with *n*-butylzinc bromide and then coupled with isopropenylzinc bromide in the presence of a catalytic amount of $Pd(PPh_3)_4$ [6] to afford the corresponding dienols **2a** (66%) and **2b** (97%). We next examined the cyclopropanation of these compounds and the use of samarium carbenoids as cyclopropanating reagents ensured complete regioselectivity with exclusive reaction at the allylic alcohol moiety[7] to give the secondary *cis*,*syn*-isopropenylcyclopropylcarbinols **3a** (71%) and **3b** (81%). As anticipated, these hydroxy-directed cyclopropanations turned out to proceed in a highly diastereoselective fashion (**3a**: *dr* ≥ 95:5; **3b**: *dr* ≥ 98:2). The relative *syn* configuration of **3b** was unambiguously assigned by X-ray crystallographic analysis of its crystalline 4-nitrobenzoate ester derivative **4**, which confirmed that the stereochemical outcome of the cyclopropanation was in agreement with literature results (Scheme 2).[7b]

In order to have access to the epimeric cyclopropylcarbinol, **3b** was oxidized to the corresponding cyclopropyl ketone **5** (82%) with PDC, and the latter was reduced with sodium borohydride in methanol to furnish the *cis*,*anti*-isopropenylcyclopropylcarbinol **3c** (76%) in a highly diastereoselective fashion (*dr* = 97:3). The stereochemical outcome of this reduction could be predicted on the basis of the known sense of additions to cyclopropyl ketones, which involve nucleophilic attack at the less crowded side of the carbonyl group in the bisected *s-cis* conformation (Scheme 3).[4]

Although this sequence allowed rapid access to the desired *cis*,*syn*- or *cis*,*anti*-isopropenylcyclopropylcarbinols, we have to point out that the overall chemical yield was lower in the case of **3a** due to the volatility of this compound. Moreover, the crucial role played by the hydroxy group during the cyclopropanation step precludes its protection in order to form less volatile derivatives. Therefore, it became apparent that this procedure is not well suited for the preparation of the *cis*-isopropenylcyclopropylmethanol

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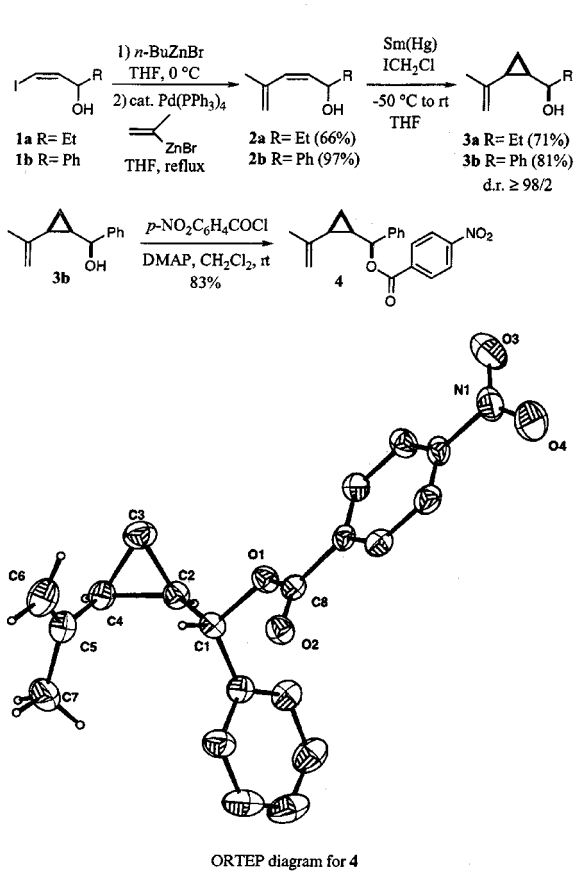
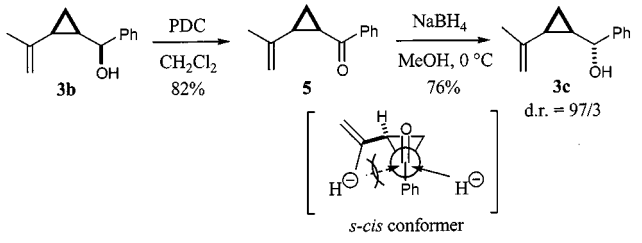


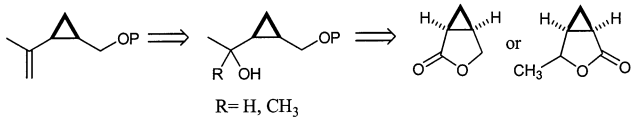
Scheme 2. Synthesis of secondary *cis,syn*-isopropenylcyclopropylcarbinols



Scheme 3. Synthesis of *cis,anti*-isopropenylcyclopropylcarbinols

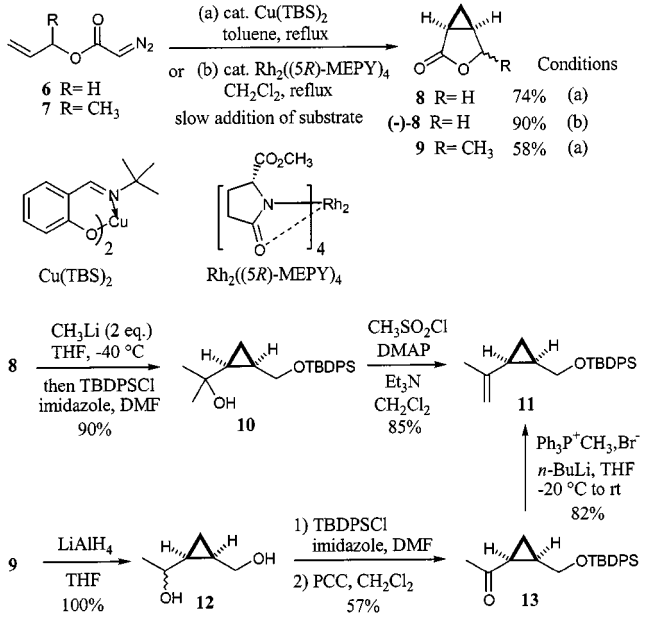
(R = H) derivatives and hence a second strategy was devised in order to achieve this goal.

The protected *cis*-isopropenylcyclopropylmethanol could be obtained from either a secondary or a tertiary cyclopropylcarbinol, which, in turn, could be obtained from bicyclic lactones, thereby ensuring the *cis* configuration of the cyclopropane ring (Scheme 4).



Scheme 4. Retrosynthesis for *cis*-isopropenylcyclopropylmethanol derivatives

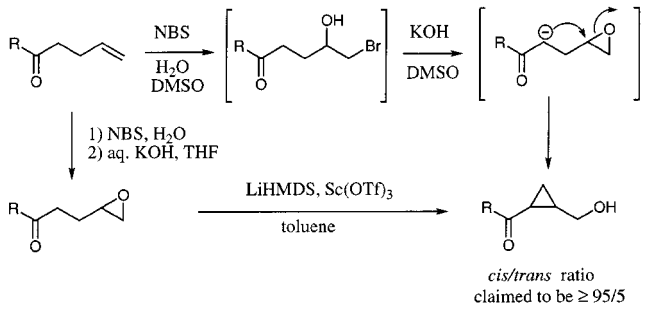
The bicyclic lactones **8** (74%) and **9** (58%; 1:1 mixture of diastereomers) were obtained by copper-catalyzed intramolecular cyclopropanation[8] of the allylic diazoacetates **6** and **7**,[9] respectively, and their transformation into the *cis*-isopropenylcyclopropane **11** was carried out according to two different routes. In the first approach, **8** was treated with two equivalents of methyllithium and then the primary lithioalkoxide was subjected to in situ silylation with *tert*-butylchlorodiphenylsilane to afford the tertiary alcohol **10** (90%). Upon treatment with excess methanesulfonyl chloride and triethylamine, **10** was cleanly dehydrated to give the *cis*-isopropenylcyclopropane **11** (85%). In the second approach, **9** was reduced with lithium aluminum hydride to give the corresponding diol **12** (100%; 1:1 mixture of diastereomers). The primary hydroxy group was silylated with *tert*-butylchlorodiphenylsilane and the resulting secondary alcohol was oxidized with PCC to give the *cis*-cyclopropyl ketone **13** (57%). The latter was subjected to a standard Wittig methylenation to afford **11** (82%). Both routes proved to be extremely convenient for the preparation of *cis*-isopropenylcyclopropane **11** on a large scale. Furthermore, according to the first route, (+)-**11** (*ee* ≥ 95%) could easily be obtained from (−)-**8** by performing the intramolecular cyclopropanation of allyl diazoacetate **6** with Doyle's $Rh_2[(5R)\text{-MEPY}]_4$ catalyst (Scheme 5).[10,11]



Scheme 5. Preparation of protected *cis*-isopropenylcyclopropylmethanol

During the course of our investigations, a third route towards *cis*-isopropenylcyclopropanes was also considered. It has been reported that successive treatment of γ-ethylenic ketones with *N*-bromosuccinimide and potassium hydroxide in DMSO affords 2-(hydroxymethyl)cyclopropyl ketones with unprecedentedly high *cis* selectivities[12] as compared to previously reported similar transformations.[13] More recently, lithium hexamethyldisilazide (LiHMDS) in combination with $Sc(OTf)_3$ has been used to induce the same 1,3-elimination from γ-epoxy ketones (Scheme 6).[14]

For the synthesis of isopropenyl- or related alkenyl-substituted cyclopropanes, this route was considered as being particularly attractive owing to its simplicity, since a simple

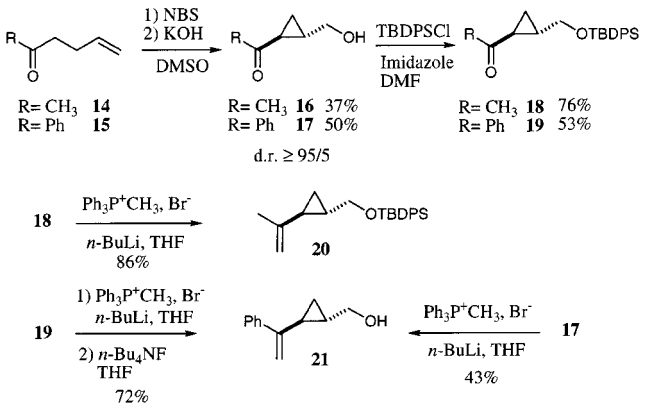


Scheme 6. Preparation of 2-(hydroxymethyl)cyclopropyl ketones

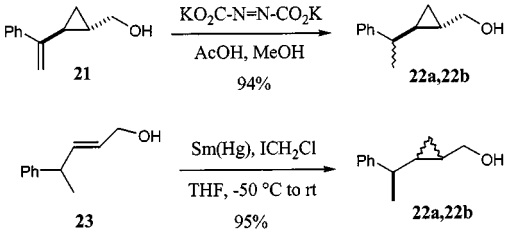
methylenation would, in principle, lead to the required structures. However, we have been able to demonstrate that the configuration of the cyclopropyl ketones generated by this process was not correctly assigned. When carried out with hex-5-en-2-one (**14**) and 1-phenylpent-4-en-1-one (**15**), the sequence described above afforded the corresponding 2-(hydroxymethyl)cyclopropyl ketones **16** (37%) and **17** (50%), respectively. Although these transformations were effectively highly diastereoselective (*dr* ≥ 95:5), we and others[14] were unable to reproduce the high yields claimed by the authors for this transformation[12] due to difficulties associated with the extraction of these polar compounds from the reaction medium. Compounds **16** and **17** were subsequently protected as *tert*-butyldiphenylsilyl ethers to give **18** (76%) and **19** (53%), respectively. The cyclopropyl ketone **18** appeared to be different from *cis*-cyclopropyl ketone **13**, which was previously synthesized from the bicyclic lactone **9** (Scheme 5). Furthermore, the spectral data of **17** and **18** are in agreement with those recently reported for the *trans* diastereomers prepared by a different route.[15] Ketone **18** was olefinated under standard Wittig conditions to give the *trans*-isopropenylcyclopropane **20** (86%), which was clearly different from the *cis*-isopropenylcyclopropane **11**.[16] Therefore, cyclopropyl ketones **16** and **18** must have a *trans* relative configuration. Similarly, cyclopropyl ketone **19** was converted into the cyclopropylcarbinol **21** (72%) by successive Wittig methylenation and desilylation with *n*-Bu_4NF. The latter could also be obtained directly from **17** (43%) by performing the olefination with excess methylenephosphorane, indicating that the Wittig reaction did not alter the relative configuration of this compound when protection of the hydroxy group was omitted (Scheme 7; for the sake of clarity, the revised configurations have been directly indicated in this Scheme).

The *trans* relative configuration of **21** was established by reducing it with excess diimide to afford the cyclopropylcarbinol **22** (94%; 1:1 mixture of diastereomers), which we have previously synthesized by means of Sm-promoted cyclopropanation of the (*E*)-allylic alcohol **23** (Scheme 8).[17] These results unambiguously confirmed the *trans* relative configuration of the cyclopropyl ketones **17** and **19**.

In order to further elucidate this discrepancy with the literature, we decided to prepare an authentic sample of *cis*-2-(hydroxymethyl)cyclopropylmethyl ketone **24**. Thus, when **13** was desilylated with *n*-Bu_4NF in THF, a clean reaction occurred, invariably leading to an equilibrium mixture of

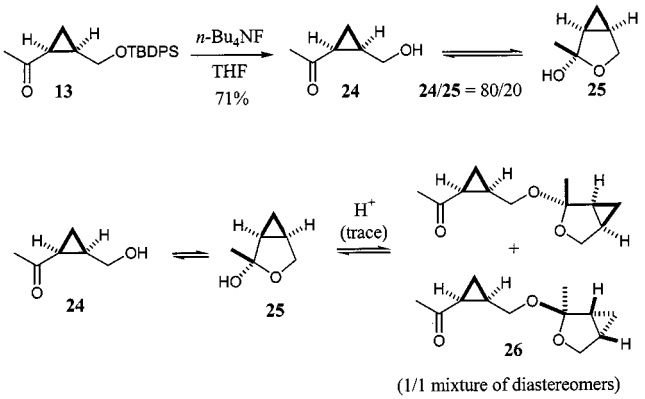


Scheme 7. Preparation of protected *trans*-isopropenylmethanol and related structures from 2-(hydroxymethyl)cyclopropyl ketones



Scheme 8. Correlation of configuration of compound **21**

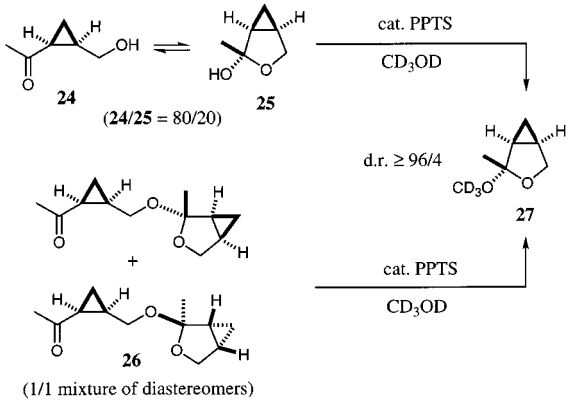
the *cis*-cyclopropyl ketone **24** and its bicyclic hemiketal **25** (71%; 80:20 inseparable mixture, single diastereomers).[18a] This mixture of **24** and **25** was found to be stable for a few months when kept as a frozen benzene solution at −23 °C. However, upon standing for several hours at room temperature or in the presence of traces of acid (especially acidic $CDCl_3$), a new mixture was obtained containing variable amounts of **24**, **25**, and the dimer **26** as a 1:1 mixture of diastereomers, with the relative configuration of the ketal stereocenter apparently perfectly controlled (Scheme 9).[18,19]



Scheme 9. Preparation and behaviour of *cis*-2-(hydroxymethyl)cyclopropylethanone

In order to confirm the structures of **25** and **26**, the equilibrium mixture of **24** and **25** was dissolved in CD_3OD and a catalytic amount of pyridinium *p*-toluenesulfonate was added. After several hours at room temperature, ^1H and ^{13}C NMR spectra indicated the complete formation of the mixed ketal **27** with methanol (single diastereomer).[18a] Un-

der the same conditions, **26** was also quantitatively converted into **27** (Scheme 10).



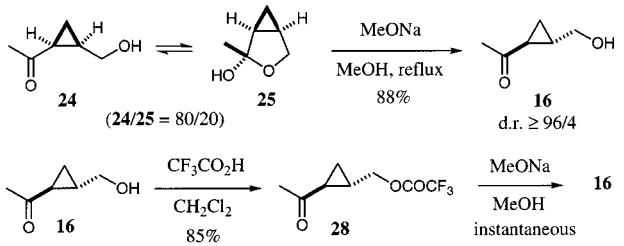
Scheme 10. Chemical behaviour of *cis*-2-(hydroxymethyl)cyclopropylethanone

Since other reactions and especially isomerizations involving 2-(hydroxymethyl)cyclopropyl ketones have also been reported in the literature,[20] we wanted to reinvestigate these results, having established the exact relative configuration of these compounds. The *cis*-cyclopropyl ketone **24** (mixture with **25**) was quantitatively converted into the *trans*-cyclopropyl ketone **16** upon treatment with sodium methoxide in refluxing methanol for several hours.[21] Contrary to what was suggested previously,[20] this result indicated that the *trans*-2-(hydroxymethyl)cyclopropyl ketones are the thermodynamically most stable isomers.[21,22] Therefore, the high degree of stereoselectivity observed in the 1,3-elimination of γ-epoxy ketones with either KOH in DMSO[12] or LiHMDS/$Sc(OTf)_3$[14] is a consequence of thermodynamic control.

It has also been reported that treatment of the cyclopropyl ketones derived from 1,3-elimination of γ-epoxy ketones with trifluoroacetic acid (TFA) in chloroform induced their so-called isomerization, whereas the reverse reaction was observed under alkaline conditions.[20] When ketone **16** was treated with excess TFA in CH_2Cl_2 at room temperature for 2−5 d, a very clean conversion into a less polar compound was observed. However, the latter proved to be the trifluoroacetate **28** formed by esterification of the OH group of **16** with TFA. Its structure could have been confused with that of an epimer of **16** by ^1H NMR owing to their great similarity and the absence of new signals, but the presence of the trifluoroacetate group was unambiguously established by IR, ^{13}C NMR, and GC-MS analyses. Consequently, treatment of the trifluoroacetate **28** with a base such as sodium methoxide obviously resulted in reversion to the initial compound **16**, owing to the great sensitivity of trifluoroacetic esters towards various bases (Scheme 11).

Conclusion

This study has enabled us to show that the relative configurations of the 2-(hydroxymethyl)cyclopropyl ketones generated by 1,3-elimination of γ-epoxy ketones were previously incorrectly assigned. We have now unambiguously established them to be *trans*, as a result of a thermodynamically controlled process. Moreover, chemical transformations which were thought to correspond to kinetically and thermodynamically controlled isomerizations were actually simple esterification and saponification reactions, which proceed without affecting the relative configurations of the corresponding cyclopropyl ketones.



Scheme 11. Reactivity of *cis*- and *trans*-2-(hydroxymethyl)cyclopropylethanone

We have devised efficient routes towards *cis*-isopropenylcyclopropanes and we are currently exploiting these compounds as synthetically useful building blocks in natural product synthesis.

Experimental Section

General Remarks: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane, DMF, toluene, and triethylamine were distilled from calcium hydride. Zinc bromide was melted, cooled under argon, and handled as a 1 M solution in anhydrous THF. − Moisture-sensitive reactions were carried out in oven-dried glassware under argon. − Analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}) plates. − Flash chromatography was performed on Merck Kieselgel 60 (230−400 mesh). − Melting points were measured with a Kofler apparatus. − IR: Perkin−Elmer 298. − Optical rotations: Perkin−Elmer 241 MC polarimeter. − Elemental analyses: Service Régional de Microanalyses de l'Université P. et M. Curie. − HRMS: Laboratoire de Spectrochimie de l'Ecole Normale Supérieure Ulm. − NMR: Bruker AC spectrometer (300 MHz and 75 MHz for ^1H and ^{13}C, respectively); chemical shifts (δ) are expressed in ppm relative to TMS (δ = 0). − MS: Mass spectra were obtained by GC/MS with a Hewlett Packard 5971 instrument operating in electron impact ionization mode at 70 eV.

(*Z*)-6-Methylhepta-4,6-dien-3-ol (2a):[23] To a solution of *n*-butylzinc bromide [prepared from *n*-butyllithium (5.30 mL, 2.5 M in hexanes, 13.1 mmol, 1.1 equiv.) and zinc bromide (13.1 mL, 1 M in THF, 13.1 mmol, 1.1 equiv.) in THF (10 mL)], a solution of **1a**[5a] (2.50 g, 11.8 mmol) in THF (7 mL) was added dropwise at 0 °C. After 20 min at this temperature, the reaction mixture was cannulated into a solution of isopropenylzinc bromide [prepared from isopropenylmagnesium bromide (36.0 mL, 0.5 M in THF, 18.0 mmol, 1.5 equiv.) and zinc bromide (18 mL, 1 M in THF, 18 mmol)]. $Pd(PPh_3)_4$ (0.420 g, 0.363 mmol, 0.03 equiv.) was added in one portion (a slightly exothermic reaction started causing a temperature increase to 28−30 °C) and, after refluxing for 1 h, the reaction mixture was cooled to room temp., poured into saturated aqueous NH_4Cl solution, and extracted with diethyl ether. The combined extracts were successively washed with saturated aqueous

$NaHCO_3$ solution, 20% aqueous $Na_2S_2O_3$ solution, and brine, dried with Na_2CO_3, filtered, and concentrated under reduced pressure. The crude material was taken up in pentane (50 mL) and the resulting mixture was refluxed, cooled to room temp., and filtered through Celite in order to remove the catalyst. After evaporation of the solvents, the crude material was purified by flash chromatography (pentane/diethyl ether, 90:10) to give 0.990 g (66%) of **2a** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3350, 3080, 1630, 1595, 1110, 1050 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 5.94 (d, *J* = 11.8 Hz, 1 H), 5.39 (dd, *J* = 11.8, 9.2 Hz, 1 H), 4.98 (d, *J* = 1.5 Hz, 1 H), 4.89 (d, *J* = 1.5 Hz, 1 H), 4.55 (m, 1 H), 2.16 (br. s, 1 H, OH), 1.87 (s, 3 H), 1.67−1.43 (2 H), 0.93 (t, *J* = 7.45 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 141.1 (s), 133.4 (d), 132.4 (d), 116.3 (t), 69.0 (d), 30.5 (t), 23.0 (q), 9.6 (q).

(*Z*)-4-Methyl-1-phenylpenta-2,4-dien-1-ol (2b): To a solution of *n*-butylzinc bromide [prepared from *n*-butyllithium (3.40 mL, 2.5 M in hexanes, 8.50 mmol, 1.1 equiv.) and zinc bromide (8.50 mL, 1 M in THF, 8.50 mmol, 1.1 equiv.) in THF (10 mL)], a solution of **1b**[5b] (2.00 g, 7.69 mmol) in THF (7 mL) was added dropwise at 0 °C. After 20 min at this temperature, the reaction mixture was cannulated into a solution of isopropenylzinc bromide [prepared from isopropenylmagnesium bromide (30.8 mL, 0.5 M in THF, 15.4 mmol, 2.0 equiv.) and zinc bromide (15.4 mL, 1 M in THF, 15.4 mmol, 2.0 equiv.)]. $Pd(PPh_3)_4$ (0.500 g, 0.433 mmol, 0.056 equiv.) was added in one portion (a slightly exothermic reaction started causing a temperature increase to 28−30 °C) and, after refluxing for 1 h, the reaction mixture was cooled to room temp., poured into saturated aqueous NH_4Cl solution, and extracted with diethyl ether. The combined extracts were successively washed with saturated aqueous $NaHCO_3$ solution, 20% aqueous $Na_2S_2O_3$ solution, and brine, dried with Na_2CO_3, filtered, and concentrated under reduced pressure. The crude material was taken up in pentane (50 mL) and the resulting mixture was refluxed, cooled to room temp., and filtered through Celite in order to remove the catalyst. After evaporation of the solvents, the crude material was purified by flash chromatography (cyclohexane/AcOEt, 90:10 to 85:15) to give 1.30 g (97%) of **2b** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3350, 3080, 3060, 3020, 1640, 1600, 1010 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.43−7.25 (5 H), 6.05 (d, *J* = 9.8 Hz, 1 H), 5.74−5.64 (2 H), 5.04 (s, 1 H), 4.93 (s, 1 H), 1.98 (br. s, 1 H, OH), 1.92 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 143.4 (s), 140.8 (s), 132.8 (d), 132.1 (d), 128.6 (d), 127.6 (d), 126.2 (d), 116.6 (t), 70.0 (d), 23.1 (q). − MS (EI); *m*/*z* (%): 174 (17) [M^+], 159 (13), 115 (10), 105 (100), 91 (11), 77 (33).

(1*R)-1-[(1*R**,2*S**)-2-Isopropenylcyclopropyl]propan-1-ol (3a):** To a suspension of samarium powder (5.90 g, 39.5 mmol, 5.0 equiv.) in THF (150 mL) were added dry $HgCl_2$ (1.72 g, 6.32 mmol, 0.8 equiv.) and **2a** (1.00 g, 7.93 mmol). To the vigorously stirred mixture, ICH_2Cl (2.90 mL, 39.5 mmol, 5.0 equiv.) was added dropwise at −50 °C. The reaction mixture was gradually allowed to warm to room temp. over a period of 2 h. It was then poured into cold saturated aqueous K_2CO_3 solution (100 mL) overlaid with diethyl ether (100 mL). After stirring for 20 min, the resulting mixture was filtered through Celite and the removed solids were thoroughly washed with diethyl ether. The aqueous layer was extracted with diethyl ether and the combined extracts were washed with brine, dried with Na_2CO_3, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/diethyl ether, 80:20) to give 0.780 g (71%) of **3a** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3360, 3080, 1645, 1100, 1035 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 4.84 (s, 1 H), 4.65 (s, 1 H), 3.07 (ddd, *J* = 8.5, 7.3, 4.0 Hz, 1 H), 1.82 (s, 3 H), 1.72 (br. s, 1 H, OH), 1.65−1.46 (3 H), 1.12 (m, 1 H), 0.96 (t, *J* = 7.3 Hz, 3 H), 0.81−0.71 (2 H). − ^{13}C NMR ($CDCl_3$): δ = 142.5 (s), 110.6 (t), 72.2 (d), 30.6 (t), 24.6 (d), 24.2 (q), 22.9 (d), 9.9 (q), 7.0 (t). − MS (EI; *m*/*z* (%): 140 (2) [M^+], 125 (32), 111 (44), 93 (67), 85 (39), 72 (66), 67 (81), 57 (100). − $C_9H_{16}O$ (140.22): calcd. C 77.09, H 11.50; found C 77.38, H 11.61.

(*S)-[(1*R**,2*S**)-2-Isopropenylcyclopropyl]phenylmethanol (3b):** To a suspension of samarium powder (4.32 g, 28.7 mmol, 5.0 equiv.) in THF (150 mL) were added dry $HgCl_2$ (1.56 g, 5.75 mmol, 1.0 equiv.) and **2b** (1.00 g, 5.75 mmol). To the vigorously stirred mixture, ICH_2Cl (2.10 mL, 28.7 mmol, 5.0 equiv.) was added dropwise at −50 °C. The reaction mixture was gradually allowed to warm to room temp. over a period of 2 h. It was then poured into cold saturated aqueous K_2CO_3 solution (150 mL) overlaid with diethyl ether (150 mL). After stirring for 20 min, the resulting mixture was filtered through Celite and the removed solids were thoroughly washed with diethyl ether. The aqueous layer was extracted with diethyl ether and the combined extracts were washed with brine, dried with Na_2CO_3, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt gradient, 90:10 to 80:20) to give 0.875 g (81%) of **3b** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3350, 3080, 3030, 1645, 1605, 1020 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.40−7.24 (5 H), 4.88 (quint., *J* = 1.5 Hz, 1 H), 4.71 (br. s, 1 H), 4.14 (m, 1 H), 1.98 (br. s, 1 H, OH), 1.57 (s, 3 H), 1.54−1.47 (2 H), 0.98−0.89 (2 H). − ^{13}C NMR ($CDCl_3$): δ = 144.2 (s), 142.7 (s), 128.3 (d), 127.6 (d), 126.4 (d), 110.5 (t), 73.7 (d), 25.8 (d), 24.6 (q), 23.1 (d), 7.9 (t). − MS (EI); *m*/*z* (%): 188 (0.6) [M^+], 170 (9) [$M^+ - H_2O$], 120 (100), 105 (23), 91 (36), 79 (14), 77 (19). − $C_{13}H_{16}O$ (188.27): calcd. C 82.94, H 8.57; found C 83.27, H 8.43.

(*S)-[(1*R**,2*S**)-2-Isopropenylcyclopropyl]phenylmethyl 4-Nitrobenzoate (4):** To a solution of **3b** (0.112 g, 0.595 mmol) and 4-dimethylaminopyridine (0.073 g, 0.597 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added 4-nitrobenzoyl chloride (0.111 g, 0.598 mmol). After 1 h at room temp., the reaction mixture was quenched by the addition of 1 M aqueous hydrochloric acid solution and extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt, 95:5) to give 0.167 g (83%) of **4** as pale-yellow crystals. Recrystallization from diethyl ether/pentane yielded colorless crystals suitable for X-ray crystallographic analysis; m.p. 97−99 °C. − IR (KBr): $\tilde{\nu}$ = 1718, 1605, 1523, 1272, 1103 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 8.28−8.21 (4 H), 7.47−7.26 (5 H), 5.65 (d, *J* = 10.0 Hz, 1 H), 4.98 (s, 1 H), 4.83 (s, 1 H), 1.79 (m, 1 H), 1.60 (m, 1 H), 1.58 (s, 3 H), 1.08 (m, 1 H), 0.97 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 164.1 (s), 150.4 (s), 141.7 (s), 140.1 (s), 136.1 (s), 130.7 (d), 128.5 (d), 128.3 (d), 127.1 (d), 123.4 (d), 111.2 (t), 78.3 (d), 24.6 (q), 23.39 (d), 23.38 (d), 8.8 (t).

(1*R,2*S**)-2-Isopropenylcyclopropyl Phenyl Ketone (5):** To a vigorously stirred mixture of **3b** (1.00 g, 5.31 mmol) and 4 Å powdered molecular sieves (4 g) in CH_2Cl_2 (40 mL) was added PDC (4.00 g, 10.6 mmol). After 3 h at room temp., the reaction mixture was filtered through Florisil (CH_2Cl_2). After evaporation of the solvent, the crude product was purified by flash chromatography (cyclohexane/diethyl ether, 90:10) to give 0.816 g (82%) of **5** as a pale-yellow oil. − IR (neat): $\tilde{\nu}$ = 3070, 3030, 1720, 1670, 1595, 1570, 1220, 1015 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 8.02 (m, 2 H), 7.56−7.42 (3 H), 4.93 (s, 1 H), 4.85 (s, 1 H), 2.92 (ddd, *J* = 9.4, 7.5, 5.6 Hz, 1 H), 2.19 (m, 1 H), 1.82 (ddd, *J* = 7.5, 5.6, 4.5 Hz, 1 H), 1.58 (s, 3 H), 1.20 (ddd, *J* = 8.1, 7.5, 4.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$):

δ = 195.8 (s), 139.2 (s), 138.3 (s), 132.4 (d), 128.3 (d), 127.9 (d), 113.8 (t), 31.7 (d), 25.4 (d), 23.3 (q), 11.4 (t).

(*R)-[(1*R**,2*S**)-2-Isopropenylcyclopropyl]phenylmethanol (3c):** To a solution of **5** (0.430 g, 2.31 mmol) in MeOH (10 mL) at 0 °C was added sodium borohydride (0.131 g, 3.46 mmol). After 1 h at room temp., the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined extracts were washed with brine, dried with Na_2CO_3, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt, 90:10) to give 0.332 g (76%) of **3c** as a waxy solid; m.p. 31 °C. − IR (neat): $\tilde{\nu}$ = 3350, 3060, 3020, 1640, 1595, 1035, 1010 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.41−7.23 (5 H), 4.96 (s, 1 H), 4.73 (s, 1 H), 4.09 (d, *J* = 9.7 Hz, 1 H), 2.00 (s, 3 H), 1.99 (br. s, 1 H, OH), 1.61 (m, 1 H), 1.41 (m, 1 H), 0.75 (m, 1 H), 0.62 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 144.5 (s), 142.8 (s), 128.3 (d), 127.3 (d), 126.0 (d), 110.8 (t), 73.7 (d), 26.2 (d), 24.3 (q), 23.6 (d), 7.6 (t). − MS (EI); *m*/*z* (%): 188 (0.2) [M^+], 170 (13) [$M^+ - H_2O$], 155 (10), 120 (100), 105 (16), 91 (44), 77 (18). − $C_{13}H_{16}O$ (188.27): calcd. C 82.94, H 8.57; found C 83.22, H 8.46.

(1*S,5*R**)-3-Oxabicyclo[3.1.0]hexan-2-one (8):**[10] To a refluxing solution of bis(*tert*-butylsalicylaldiminato)copper(II) (0.303 g, 0.730 mmol, 0.05 equiv.) in toluene (100 mL), a solution of **6** (1.84 g, 14.6 mmol) in toluene (50 mL) was added over a period of 3 h. The resulting mixture was refluxed for a further 30 min and then allowed to cool to room temp. It was diluted with methanol and then concentrated under reduced pressure (bath temperature below 30 °C). When most of the solvent had evaporated, further methanol was added and the process was repeated. The crude material was purified by flash chromatography (pentane/diethyl ether, 30:70) to give 1.10 g (74%) of **8** as a yellow liquid. − IR (neat): $\tilde{\nu}$ = 3080, 1770, 1180, 1035 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 4.36 (dd, *J* = 9.4, 4.8 Hz, 1 H), 4.23 (d, *J* = 9.4 Hz, 1 H), 2.25 (m, 1 H), 2.07 (m, 1 H), 1.28 (m, 1 H), 0.88 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 176.4 (s), 69.4 (t), 17.5 (d), 17.3 (d), 12.2 (t). − MS (EI); *m*/*z* (%): 98 (100) [M^+], 70 (40), 68 (73), 55 (35), 53 (20).

(1*S*,5*R*)-3-Oxabicyclo[3.1.0]hexan-2-one [(−)-8]:[10] To a refluxing solution of Doyle's catalyst Rh_2[(5*R*)-MEPY]$_4$ (0.050 g, 0.055 mmol, 0.001 equiv.) in freshly distilled CH_2Cl_2 (150 mL), a solution of **6** (6.50 g, 51.5 mmol) in freshly distilled CH_2Cl_2 (350 mL) was added over a period of 30 h. The solvent was then distilled off and the crude material was purified by flash chromatography (pentane/diethyl ether gradient, 40:60 to 30:70) to give 4.55 g (90%) of (−)-**8** as a yellow oil. − $[\alpha]_D^{20}$ = −65.0 (*c* = 1.0, $CHCl_3$) (*ee* ≥ 95%).[10,11]

2-[(1*S*,2*R*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}cyclopropyl]-propan-2-ol [(+)-10]: To a solution of (−)-**8** (1.00 g, 10.2 mmol) in THF at −40 °C was added methyllithium (14.0 mL, 1.6 M in diethyl ether, 22.4 mmol, 2.2 equiv.). After 15 min at this temperature, a solution of *tert*-butylchlorodiphenylsilane (3.45 mL, 13.2 mmol, 1.3 equiv.) and imidazole (1.80 g, 26.5 mmol, 2.6 equiv.) in DMF (5 mL) was added dropwise and the reaction mixture was allowed to warm to room temp. After 1 h, it was quenched by the addition of dilute aqueous NH_4Cl solution and extracted with cyclohexane/CH_2Cl_2 (9:1). The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/CH_2Cl_2, 90:10) to give 3.4 g (90%) of (+)-**10** as a colorless oil. − $[\alpha]_D^{20}$ = +15.2 (*c* = 2.1, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3430, 3060, 3040, 3020, 1110, 1065, 1045 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.74−7.68 (4 H), 7.42−7.34 (6 H), 4.12 (dd, *J* = 11.6, 6.0 Hz, 1 H), 3.69 (dd, *J* = 11.6, 9.8 Hz, 1 H), 3.19 (s, 1 H, OH), 1.47 (s, 3 H), 1.26 (s, 3 H), 1.24−1.06 (2 H), 1.06 (s, 9 H), 0.65 (m, 1 H), 0.39 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 135.5 (d), 134.8 (d), 133.2 (s), 133.1 (s), 129.7 (d), 129.4 (d), 127.7 (d), 127.65 (d), 127.6 (d), 69.6 (s), 64.9 (t), 31.8 (q), 29.7 (q), 27.9 (d), 26.7 (q), 19.0 (s), 18.5 (d), 7.5 (t). − MS (EI); *m*/*z* (%): 353 (1) [$M^+ - CH_3$], 311 (5) [$M^+ - t$Bu], 199 (100), 139 (26), 95 (21), 69 (76). − $C_{23}H_{32}O_2Si$ (368.59): calcd. C 74.95, H 8.75; found C 75.03, H 8.71.

(1*R*,2*S*)-1-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-isopropenylcyclopropane [(+)-11]: To a solution of (+)-**10** (2.5 g, 6.8 mmol), 4-dimethylaminopyridine (0.99 g, 8.11 mmol, 1.2 equiv.) and triethylamine (14.1 mL, 10.1 mmol, 15.0 equiv.) in CH_2Cl_2 (60 mL), methanesulfonyl chloride (5.2 mL, 67.5 mmol, 10.0 equiv.) was added dropwise at 0 °C. After 3 h at this temperature, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/CH_2Cl_2 gradient, 100:0 to 90:10) to give 2.0 g (85%) of (+)-**11** as a colorless oil. − $[\alpha]_D^{20}$ = +10.7 (*c* = 1.025, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3070, 1645, 1110, 1065 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.71−7.65 (4 H), 7.40−7.33 (6 H), 4.79 (s, 1 H), 4.51 (s, 1 H), 3.64 (dd, *J* = 10.9, 5.5 Hz, 1 H), 3.41 (dd, *J* = 10.9, 8.9 Hz, 1 H), 1.90 (s, 3 H), 1.48 (m, 1 H), 1.28 (m, 1 H), 1.05 (s, 9 H), 0.63 (m, 1 H), 0.36 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 142.9 (s), 135.6 (d), 134.1 (s), 129.4 (d), 127.55 (d), 127.5 (d), 110.4 (t), 63.2 (t), 26.8 (q), 24.3 (q), 22.9 (d), 19.7 (d), 19.2 (s), 6.5 (t). − MS (EI); *m*/*z* (%): 350 (1) [M^+], 293 (73) [$M^+ - t$Bu], 251 (60), 237 (45), 225 (50), 199 (100), 183 (44). − $C_{23}H_{30}OSi$ (350.58): calcd. C 78.80, H 8.63; found C 78.82, H 8.65.

(1*S,4*R***S**,5*R**)-4-Methyl-3-oxabicyclo[3.1.0]hexan-2-one (9):** To a refluxing solution of bis(*tert*-butylsalicylaldiminato)copper(II) (6.00 g, 14.4 mmol, 0.05 equiv.) in toluene (2.5 L), a solution of **7** (40.1 g, 286 mmol) in toluene (500 mL) was added over a period of 4 h. The resulting mixture was refluxed for a further 30 min, cooled to room temp., and concentrated under reduced pressure. The crude material was purified by filtration through silica gel (cyclohexane/diethyl ether gradient, 70:30 to 30:70) to give 18.6 g (58%) of **9** as a yellow liquid (1:1 mixture of diastereomers). − IR (neat): $\tilde{\nu}$ = 3080, 1760, 1290, 1050, 1020 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 4.79 (qd, *J* = 6.1, 4.7 Hz, 1 H), 4.48 (q, *J* = 6.2 Hz, 1 H), 2.24 (m, 1 H), 2.11−2.04 (3 H), 1.42 (d, *J* = 6.1 Hz, 3 H), 1.36 (d, *J* = 6.2 Hz, 3 H), 1.26 (m, 1 H), 1.12 (m, 1 H), 0.92 (m, 1 H), 0.88 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 176.1 (s), 175.7 (s), 77.3 (d), 75.5 (d), 23.5 (d), 21.8 (q), 22.0 (d), 18.5 (d), 17.5 (d), 17.5 (q), 12.3 (t), 8.5 (t). − MS (EI); *m*/*z* (%): First diastereomer: 112 (18) [M^+], 97 (100) [$M^+ - CH_3$], 53 (15); second diastereomer: 112 (34) [M^+], 97 (100) [$M^+ - CH_3$], 68 (21), 55 (22), 53 (25).

1(*R*S**)-[(1*S**,2*R**)-2-(Hydroxymethyl)cyclopropyl]ethanol (12):** To a stirred suspension of $LiAlH_4$ (3.38 g, 89.2 mmol, 1.0 equiv.) in dry THF (200 mL), **9** (10.0 g, 89.2 mmol) was added dropwise at 0 °C. After 20 min at this temperature, the reaction mixture was cautiously quenched by the dropwise addition of water (3.4 mL), a 15% aqueous solution of NaOH (3.4 mL), and further water (10.2 mL). After 1 h at room temp., the resulting mixture was filtered through Celite. The removed solids were triturated three times with boiling THF, the combined hot solutions were filtered through Celite, and the filtrate was concentrated under reduced pressure to give 10.4 g (100%) of **12** as a white solid (1:1 mixture of diastereomers). An analytical sample of each diastereomer was obtained by flash chromatography (cyclohexane/AcOEt gradient, 20:80 to 0:100). − Less polar diastereomer: R_f = 0.24 (cyclohexane/AcOEt, 10:90). −

IR ($CHCl_3$): $\tilde{\nu}$ = 3320, 3060, 1190, 1170, 1115 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 3.75 (dd, *J* = 11.2, 7.1 Hz, 1 H), 3.64−3.55 (2 H), 1.72 (br. m, 1 H, OH), 1.68 (br. s, 1 H, OH), 1.27 (m, 1 H), 1.08 (m, 1 H), 0.80 (m, 1 H), 0.33 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 68.0 (d), 62.3 (t), 23.9 (d), 23.7 (q), 18.3 (d), 8.0 (t). − More polar diastereomer: R_f = 0.12 (cyclohexane/AcOEt, 10:90). − IR ($CHCl_3$): $\tilde{\nu}$ = 3340, 3060, 1095, 1070, 1030, 1010 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 4.53 (br. s, 2 H, OH), 4.10 (m, 1 H), 3.44 (m, 1 H), 3.23 (dd/pseudo t, *J* = 11.3 Hz, 1 H), 1.35 (d, *J* = 6.2 Hz, 3 H), 1.28 (m, 1 H), 1.05 (m, 1 H), 0.78 (m, 1 H), 0.17 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 68.9 (d), 62.9 (t), 23.6 (d), 22.5 (q), 17.5 (d), 8.4 (t).

1-[(1*S,2*R**)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}cyclopropyl]-ethanone (13):** To a solution of **12** (1:1 mixture of diastereomers) (8.6 g, 74 mmol) and imidazole (11.1 g, 163 mmol, 2.2 equiv.) in DMF (20 mL), was added *tert*-butylchlorodiphenylsilane (19.4 mL, 74.0 mmol, 1.0 equiv.). After 1 h at room temp., the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with cyclohexane/CH_2Cl_2 (9:1). The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was dissolved in CH_2Cl_2 (400 mL), powdered 4 Å molecular sieves (50 g) and PCC (22.3 g, 103 mmol, 1.4 equiv.) were added, and after 90 min at room temp. the reaction mixture was filtered through silica gel (CH_2Cl_2) to give 14.9 g (57%) of **13** as white crystals; m.p. 58 °C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 3040, 1690, 1585, 1155, 1105, 1070 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.68−7.61 (4 H), 7.44−7.36 (6 H), 3.87 (dd, *J* = 11.1, 5.2 Hz, 1 H), 3.51 (dd, *J* = 11.1, 9.8 Hz, 1 H), 2.36 (s, 3 H), 2.16 (m, 1 H), 1.67 (m, 1 H), 1.14 (m, 1 H), 1.02 (s, 9 H), 0.87 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 206.1 (s), 135.4 (d), 133.9 (s), 133.5 (s), 129.5 (d), 127.5 (d), 61.4 (t), 31.7 (q), 26.7 (q), 26.5 (d), 25.4 (d), 19.1 (s), 11.6 (t). − MS (EI); *m*/*z* (%): 295 (80) [M^+ − *t*Bu], 239 (23), 225 (100), 199 (31), 191 (23), 183 (65), 165 (39).

(1*S,2*R**)-1-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-isopropenylcyclopropane (11) from 15:** To a solution of methyltriphenylphosphonium bromide (20.7 g, 58.0 mmol) in THF (200 mL), *n*-butyllithium (23.2 mL, 2.5 M in hexanes, 58.0 mmol) was added dropwise at 0 °C. After 15 min at this temperature, a solution of **13** (12.0 g, 34.1 mmol) in THF (50 mL) was added dropwise. After 3 h at room temp., the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The solid residue was taken up in pentane and triturated several times. After filtration through Celite and evaporation of the solvent under reduced pressure, the crude material was purified by flash chromatography (cyclohexane/diethyl ether, 95:5) to give 9.8 g (82%) of **11** as a colorless oil.

1-[(1*S,2*S**)-2-(Hydroxymethyl)cyclopropyl]ethanone (16):** To a solution of hex-5-en-2-one **14** (5.0 mL, 43 mmol) in DMSO (150 mL) containing water (1.5 mL), was added *N*-bromosuccinimide (8.4 g, 47 mmol, 1.1 equiv.) followed, after 15 min, by potassium hydroxide (12.1 g, 216 mmol, 5.0 equiv.). After 16 h at room temp., the reaction mixture was diluted with water, neutralized with AcOH, and extracted with AcOEt. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt gradient, 40:60 to 30:70) to give 1.84 g (37%) of **16** as a slightly yellow oil. − R_f = 0.13 (cyclohexane/AcOEt, 40:60). − IR (neat): $\tilde{\nu}$ = 3400, 1690, 1180, 1030 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 3.66 (dd, *J* = 11.5, 5.7 Hz, 1 H), 3.41 (dd, *J* = 11.5, 7.0 Hz, 1 H), 3.15 (br. s, 1 H, OH), 2.25 (s, 3 H), 1.94 (m, 1 H), 1.72 (m, 1 H), 1.24 (m, 1 H), 0.93 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 208.4 (s), 64.1 (t), 30.0 (d), 29.4 (d), 26.7 (q), 14.9 (t).

[(1*S,2*S**)-(2-Hydroxymethyl)cyclopropyl]phenylmethanone (17):**[15] To a solution of 1-phenylpent-4-en-1-one (**15**) (12.5 g, 78.1 mmol) in DMSO (400 mL), containing water (4 mL), was added *N*-bromosuccinimide (15.3 g, 85.8 mmol, 1.1 equiv.) followed, after 15 min, by potassium hydroxide (21.9 g, 391 mmol, 5.0 equiv.). After 15 h at room temp., the reaction mixture was diluted with water, neutralized with AcOH, and extracted with AcOEt. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt, 85:15) to give 6.98 g (50%) of **17** as an orange oil. − IR (neat): $\tilde{\nu}$ = 3480, 1710, 1680, 1595, 1580, 1220, 1025 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.97 (m, 2 H), 7.50 (m, 1 H), 7.39 (m, 2 H), 3.96 (br. s, 1 H, OH), 3.72 (dd, *J* = 11.5, 5.5 Hz, 1 H), 3.49 (dd, *J* = 11.5, 6.8 Hz, 1 H), 2.65 (m, 1 H), 1.88 (m, 1 H), 1.41 (m, 1 H), 1.04 (ddd, *J* = 8.1, 6.2, 3.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 200.0 (s), 137.3 (s), 132.6 (d), 128.2 (d), 127.8 (d), 63.7 (t), 27.6 (d), 22.5 (d), 15.6 (t). − MS (EI); *m*/*z* (%): 176 (4) [M^+], 158 (32) [$M^+ - H_2O$], 157 (11), 145 (13), 120 (27), 115 (10), 105 (100), 77 (57), 55 (15).

1-[(1*S,2*S**)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}cyclopropyl]-ethanone (18):**[15] To a solution of **16** (3.20 g, 28.1 mmol) and imidazole (4.20 g, 61.7 mmol, 2.2 equiv.) in DMF (30 mL), was added *tert*-butylchlorodiphenylsilane (8.10 mL, 30.9 mmol, 1.1 equiv.). After 2 h at room temp., the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with cyclohexane/CH_2Cl_2 (9:1). The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/diethyl ether, 90:10) to give 7.50 g (76%) of **18** as a colorless oil, slightly contaminated with *tert*-butyldiphenylsilanol. − IR (neat): $\tilde{\nu}$ = 3060, 3040, 1685, 1110, 1080 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.66−7.63 (4 H), 7.46−7.35 (6 H), 3.77 (dd, *J* = 10.9, 4.7 Hz, 1 H), 3.51 (dd, *J* = 10.9, 6.1 Hz, 1 H), 2.18 (s, 3 H), 1.85 (m, 1 H), 1.67 (m, 1 H), 1.19 (m, 1 H), 1.06 (s, 9 H), 0.88 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 208.0 (s), 135.5 (d), 133.5 (s), 133.45 (s), 129.7 (d), 127.7 (d), 64.6 (t), 30.3 (q), 26.9 (d), 26.8 (q), 26.3 (d), 19.2 (s), 14.6 (t). − MS (EI); *m*/*z* (%): 295 (100) [M^+ − *t*Bu], 265 (71), 251 (32), 225 (34), 217 (50), 199 (57), 197 (18), 187 (32), 183 (34), 181 (23), 139 (15).

(1*S,2*S**)-1-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-isopropenylcyclopropane (20):** To a solution of methyltriphenylphosphonium bromide (6.11 g, 17.1 mmol) in THF (80 mL), *n*-butyllithium (6.80 mL, 2.5 M in hexanes, 17.0 mmol) was added dropwise at 0 °C. After 20 min at this temperature, a solution of **18** (5.00 g, 14.2 mmol) in THF (25 mL) was added dropwise. After a further 1 h at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The solid residue was taken up in pentane and triturated several times. After filtration through Celite and evaporation of the solvent under reduced pressure, the crude material was purified by flash chromatography (cyclohexane/diethyl ether, 97:3) to give 4.30 g (86%) of **20** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3070, 3050, 1650, 1640, 1590, 1430, 1110, 1070 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.69−7.66 (4 H), 7.42−7.34 (6 H), 4.65 (br. s, 2 H), 3.62 (dd, *J* = 10.7, 5.8 Hz, 1 H), 3.55 (dd, *J* = 10.7, 6.2 Hz, 1 H), 1.64 (s, 3 H), 1.25 (m, 1 H), 1.14 (m, 1 H), 1.05 (s, 9 H), 0.68 (m, 1 H), 0.51 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 145.7 (s), 135.6 (d), 134.0 (s), 129.6 (d), 127.6 (d), 108.1 (t), 66.8 (t), 26.9 (q), 23.1 (d), 21.5 (d), 20.8 (q), 19.2 (s), 9.8 (t). − MS (EI); *m*/*z* (%): 350 (0.4) [M^+], 293 (74) [$M - t Bu^+$], 265

(22) 263 (20), 252 (24), 251 (100), 239 (20), 225 (25), 221 (21), 215 (24), 199 (81), 197 (24), 185 (30), 183 (35), 181 (26). − $C_{23}H_{30}OSi$ (350.57): calcd. C 78.80, H 8.62; found C 78.81, H 8.65.

[(1*S,2*S**)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}cyclopropyl]-phenylmethanone (19):** To a solution of **17** (0.300 g, 1.70 mmol) and imidazole (0.255 g, 3.74 mmol, 2.2 equiv.) in DMF (5 mL), was added *tert*-butylchlorodiphenylsilane (0.49 mL, 1.87 mmol, 1.1 equiv.). After 1 h at room temp., the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with cyclohexane/CH_2Cl_2 (9:1). The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt, 96:4) to give 0.373 g (53%) of **19** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3070, 1670, 1220, 1110, 1075 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 8.00−7.97 (m, 2 H), 7.69−7.66 (4 H), 7.52−7.32 (9 H), 3.92 (dd, *J* = 10.9, 4.6 Hz, 1 H), 3.62 (dd, *J* = 10.9, 6.3 Hz, 1 H), 2.65 (m, 1 H), 1.86 (m, 1 H), 1.48 (m, 1 H), 1.07 (m, 1 H), 1.07 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 199.4 (s), 137.9 (s), 135.4 (d), 133.4 (s), 132.5 (d), 129.6 (d), 128.3 (d), 128.0 (d), 127.6 (d), 67.8 (t), 27.7 (d), 26.7 (q), 22.5 (d), 19.1 (s), 14.6 (t). − MS (EI); *m*/*z* (%): 357 (100) [M^+ − *t*Bu], 327 (33), 249 (11), 227 (13), 225 (11), 223 (20), 199 (35), 183 (17), 117 (17), 105 (21), 77 (24).

[(1*S,2*S**)-2-(1-Phenylethenyl)cyclopropyl]methanol (21) from 17:** To a solution of methyltriphenylphosphonium bromide (1.62 g, 4.25 mmol) in THF (15 mL), *n*-butyllithium (1.80 mL, 2.5 M in hexanes, 4.50 mmol) was added dropwise at 0 °C. After 10 min at this temperature, a solution of **17** (0.320 g, 1.82 mmol) in THF (5 mL) was added dropwise. After 30 min at room temp., the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The solid residue was taken up in pentane and triturated several times. After filtration through Celite and evaporation of the solvent under reduced pressure, the crude material was purified by flash chromatography (CH_2Cl_2/AcOEt gradient, 90:10 to 80:20) to give 0.136 g (43%) of **21** as a colorless oil.

[(1*S,2*S**)-2-(1-Phenylethenyl)cyclopropyl]methanol (21) from 19:** To a solution of methyltriphenylphosphonium bromide (0.65 g, 1.82 mmol) in THF (10 mL), *n*-butyllithium (0.73 mL, 2.5 M in hexanes, 1.82 mmol) was added dropwise at 0 °C. After 10 min at this temperature, a solution of **19** (0.300 g, 0.725 mmol) in THF (5 mL) was added dropwise. After 30 min at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The solid residue was taken up in pentane and triturated several times. After filtration through Celite and evaporation of the solvent under reduced pressure, the crude material was dissolved in THF (2 mL) and *n*-Bu_4NF (1.4 mL, 1 M in THF, 1.4 mmol) was added. After 1 h at room temp., the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether. The combined extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2/AcOEt, 90:10) to give 0.092 g (72%) of **21** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 3330, 3080, 3050, 1620, 1595, 1570, 1030 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.56 (m, 2 H), 7.36−7.24 (3 H), 5.28 (d, *J* = 1.0 Hz, 1 H), 4.95 (dd, *J* = 1.1, 1.0 Hz, 1 H), 3.64 (dd, *J* = 13.5, 6.7 Hz, 1 H), 3.61 (dd, *J* = 13.5, 7.0 Hz, 1 H), 1.70 (br. s, 1 H, OH), 1.59 (m, 1 H), 1.32 (m, 1 H), 0.88 (ddd, *J* = 8.4, 5.5, 4.8 Hz, 1 H), 0.78 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 148.1 (s), 141.4 (s), 128.2 (d), 127.5 (d), 126.0 (d), 109.8 (t), 66.5 (t), 23.2 (d), 21.5 (d), 11.4 (t). − MS (EI); *m*/*z* (%): 174 (21) [M^+], 143 (36), 141 (34), 130 (61), 129 (100), 128 (76), 118 (24), 115 (62), 103 (20), 91 (27), 77 (21).

Correlation of Configuration for Compound 21

Reduction of 21

(1*S,2*R**)-2-[(1*R***S**)-1-Phenylethyl]cyclopropanemethanol (22):** To a suspension of **21** (0.080 g, 0.459 mmol) and potassium azodicarboxylate (1.36 g, 7.01 mmol, 15 equiv.) in absolute ethanol (5 mL), a solution of acetic acid (0.47 mL, 8.30 mmol) in absolute ethanol (5 mL) was added over a period of 1 h at 70 °C. The reaction mixture was then cooled to room temp., concentrated under reduced pressure, and the residue was taken up in diethyl ether. The precipitated salts were removed by filtration through a short plug of silica gel (diethyl ether), and the filtrate was concentrated under reduced pressure to give 76 mg (94%) of **22** as a colorless oil (1:1 inseparable mixture of diastereomers).

Cyclopropanation of 23

(1*S*R**,2*R***S**)-2-[(1*R**)-1-Phenylethyl]cyclopropanemethanol (22):** To a suspension of samarium powder (0.930 g, 6.18 mmol, 5.0 equiv.) in THF (20 mL) was added dry $HgCl_2$ (0.270 g, 0.994 mmol, 0.8 equiv.) and **23** (0.200 g, 1.23 mmol). To the vigorously stirred mixture, ICH_2Cl (0.450 mL, 6.18 mmol, 5.0 equiv.) was added dropwise at −50 °C. The reaction mixture was then allowed to warm to room temp. over a period of 1 h. After a further 1 h at room temp., it was poured into cold saturated aqueous K_2CO_3 solution (50 mL) overlaid with diethyl ether (50 mL). After stirring for 10 min, the resulting mixture was filtered through Celite and the removed solids were thoroughly washed with diethyl ether. The aqueous layer was extracted with diethyl ether and the combined extracts were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/AcOEt, 85:15) to give 0.205 g (95%) of **22** as a colorless oil (1:1 inseparable diastereomeric mixture). Spectral data are given for each diastereomer of which authentic samples have previously been prepared.[17]

(1*S,2*R**)-2-[(1*R**)-1-Phenylethyl]cyclopropanemethanol:** IR (neat): $\tilde{\nu}$ = 3340, 3050, 1600, 1490, 1050 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.22−7.05 (5 H), 3.20 (d, *J* = 7.0 Hz, 2 H), 2.00 (m, 1 H), 1.64 (s, 1 H, OH), 1.22 (d, *J* = 7.3 Hz, 3 H), 0.78 (m, 2 H), 0.43−0.34 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 146.8 (s), 128.2 (d), 126.7 (d), 125.9 (d), 66.4 (t), 43.2 (d), 24.6 (d), 21.1 (q), 20.5 (d), 9.9 (t). − MS (EI); *m*/*z* (%): 158 (17) [M^+ − H_2O], 143 (15), 118 (90), 117 (100), 115 (16), 106 (52), 105 (79), 91 (29). − $C_{12}H_{16}O$ (176.26): calcd. C 81.77, H 9.15; found C 81.72, H 9.18.

(1*R,2*S**)-2-[(1*R**)-1-Phenylethyl]cyclopropanemethanol:** IR (neat): $\tilde{\nu}$ = 3340, 3050, 3020, 1600, 1490, 1050 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.26−7.10 (5 H), 3.42 (d, *J* = 7.0 Hz, 2 H), 2.05 (m, 1 H), 1.57 (s, 1 H, OH), 1.28 (d, *J* = 7.0 Hz, 3 H), 0.94 (m, 1 H), 0.80 (m, 1 H), 0.41−0.29 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 146.6 (s), 128.3 (d), 126.9 (d), 125.9 (d), 66.9 (t), 43.3 (d), 24.6 (d), 21.5 (q), 21.3 (d), 9.7 (t). − MS (EI); *m*/*z* (%): 158 (5) [M^+ − H_2O], 143 (18), 132 (47), 118 (84), 117 (100), 115 (26), 106 (60), 105 (82), 104 (23), 103 (19), 91 (41), 78 (10), 77 (15). − $C_{12}H_{16}O$ (176.26): calcd. C 81.77, H 9.15; found C 81.70, H 9.20.

1-[(1*S,2*R**)-2-(Hydroxymethyl)cyclopropyl]ethanone (24) and (1*S**,2*S**,5*R**)-2-Methyl-3-oxabicyclo[3.1.0]hexan-2-ol (25):** To a solution of **13** (1.47 g, 4.17 mmol) in THF (2 mL) was added *n*-Bu_4NF (6.25 mL, 1 M in THF, 6.25 mmol, 1.5 equiv.). After 1 h at

room temp., the reaction mixture was concentrated under reduced pressure. The crude material was taken up in diethyl ether and the precipitated salts were filtered off by passage through Celite and thoroughly washed with further ether. The combined filtrate and washings were concentrated under reduced pressure and the residue was immediately purified by flash chromatography (cyclohexane/AcOEt gradient, 30:70 to 10:90) to give 0.338 g (71%) of an inseparable equilibrium mixture of **24** and **25** (80:20 ratio). This product could be stored for several months as a frozen benzene solution at −23 °C without a change in its composition. − R_f = 0.20 (cyclohexane/AcOEt, 40:60). − IR (neat): $\tilde{\nu}$ = 3400, 3010, 1690, 1170, 1030 cm^{-1}. − **24:** ^1H NMR ($CDCl_3$): δ = 3.90 (dd, *J* = 11.8, 4.4 Hz, 1 H), 3.64 (dd, *J* = 11.8, 8.4 Hz, 1 H), 2.35 (s, 3 H), 2.21 (br. s, 1 H, OH), 2.13 (m, 1 H), 1.72 (m, 1 H), 1.26 (m, 1 H), 1.12 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 208.1 (s), 58.8 (t), 31.5 (q), 26.5 (d), 25.2 (d), 12.5 (t). − **25:** ^1H NMR ($CDCl_3$): δ = 3.99 (dd, *J* = 8.1, 2.6 Hz, 1 H), 3.79 (d, *J* = 8.1 Hz, 1 H), 2.21 (br. s, 1 H, OH), 1.68−1.61 (2 H), 1.49 (s, 3 H), 0.61 (m, 1 H), 0.24 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 103.9 (s), 67.4 (t), 25.2 (d), 23.1 (q), 15.7 (d), 7.2 (t).

1-[(1*S,2*R**)-2-({[(1*S***R**,2*S***R**,5*R***S**)-2-Methyl-3-oxabicyclo[3.1.0]hexan-2-yl]oxy}methyl)cyclopropyl]ethanone (26):** Prolonged storage of the above equilibrium mixture of **24** and **25** at room temperature or exposure to traces of acid led to the formation of variable amounts of **26** (1:1 mixture of diastereomers), which could be isolated by flash chromatography (cyclohexane/AcOEt, 80:20). − R_f = 0.53 (cyclohexane/AcOEt, 40:60). − IR (neat): $\tilde{\nu}$ = 3450, 1695, 1170, 1160, 1130, 1040 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 3.89 (d, *J* = 8.1 Hz, 1 H), 3.81 (dd, *J* = 7.7, 5.1 Hz, 1 H), 3.80−3.67 (4 H), 3.36 (dd/pseudo t, *J* = 9.9 Hz, 1 H), 3.19 (dd/pseudo t, *J* = 9.9 Hz, 1 H), 2.32 (s, 2 × 3 H), 2.19−2.11 (2 H), 1.74−1.51 (6 H), 1.37 (s, 3 H), 1.29 (s, 3 H), 1.26−1.16 (2 H), 1.05−0.87 (2 H), 0.58−0.51 (2 H), 0.23−0.16 (2 H). − ^{13}C NMR ($CDCl_3$): δ = 206.1 (s), 206.0 (s), 107.2 (s), 107.1 (s), 69.0 (t), 68.5 (t), 58.6 (t), 58.55 (t), 31.7 (q, 2C), 26.0 (d), 25.8 (d), 25.5 (d), 25.3 (d), 24.0 (d), 23.9 (d), 19.8 (q), 19.0 (q), 16.3 (d), 16.1 (d), 12.0 (t), 11.7 (t), 7.3 (t), 7.1 (t).

(1*S,2*S**,5*R**)-2-([$^2H_3$]Methoxy)-2-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (27)**

Preparation from 24 and 25: To a solution of **24** and **25** (4:1 mixture) (42 mg, 0.37 mmol) in CD_3OD (0.8 mL) was added pyridinium *p*-toluenesulfonate (ca. 2 mg, 8 μmol). After 36 h, NMR analysis of the reaction mixture indicated complete conversion to **27**.

Preparation from 26: To a solution of **26** (62 mg, 0.27 mmol) in CD_3OD (0.8 mL) was added pyridinium *p*-toluenesulfonate (ca. 2 mg, 8 μmol). After 36 h, NMR analysis of the reaction mixture indicated complete conversion to **27**. − ^1H NMR (CD_3OD): δ = 4.89 (s, HOD), 3.87 (dd, *J* = 8.1, 2.6 Hz, 1 H), 3.75 (d, *J* = 8.1 Hz, 1 H), 1.74−1.65 (2 H), 1.36 (s, 3 H), 0.64 (m, 1 H), 0.22 (m, 1 H). − ^{13}C NMR (CD_3OD): δ = 109.1 (s), 70.0 (t), 49.1 (s) (overlapped with solvent signal), 27.1 (d), 19.3 (q), 17.3 (d), 8.1 (t).

Base-Induced Isomerization of 24 to 16: To a solution of **24** and **25** (4:1 mixture) (0.100 g, 0.877 mmol) in dry methanol (5 mL) was added sodium methoxide (0.332 g, 6.11 mmol, 7.0 equiv.). After refluxing for 12 h, the reaction mixture was concentrated under reduced pressure. The crude material was taken up in diethyl ether and filtered through silica gel (diethyl ether) to give 88 mg (88%) of **16** as a colorless liquid (*trans*/*cis* ≥ 95:5).

[(1*S,2*S**)-2-Acetylcyclopropyl]methyl Trifluoroacetate (28):** To a solution of **16** (0.250 g, 2.19 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.840 mL, 10.9 mmol, 5.0 equiv.). After 4 d at room temp., solid potassium carbonate was added to neutralize the excess acid. The resulting mixture was filtered through a short plug of Celite, the removed solids were rinsed with CH_2Cl_2, and the combined filtrate and washings were concentrated under reduced pressure. The crude material was immediately purified by rapid filtration through silica gel (cyclohexane/AcOEt, 70:30) to give 0.392 g (85%) of **28** as a colorless liquid. − R_f = 0.67 (cyclohexane/AcOEt, 40:60). − IR (neat): $\tilde{\nu}$ = 3010, 1790, 1710, 1350, 1220, 1160 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 4.35 (dd, *J* = 11.6, 6.5 Hz, 1 H), 4.14 (dd, *J* = 11.6, 7.9 Hz, 1 H), 2.26 (s, 3 H), 2.04 (m, 1 H), 1.85 (m, 1 H), 1.34 (m, 1 H), 0.97 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 206.1 (s), 157.4 (s, $COCF_3$, J_{C-F} = 45 Hz), 114.4 (s, CF_3, J_{C-F} = 286 Hz), 69.7 (t), 30.5 (q), 26.6 (d), 21.7 (d), 14.9 (t). − MS (EI); *m*/*z* (%): 210 (0.4) [M^+], 167 (30) [$M^+ - CH_3CO$], 103 (30), 97 (58), 96 (87) [$M^+ - CF_3COOH$], 95 (52), 83 (89), 81 (77), 69 (100), 55 (59), 54 (26), 53 (64).

Saponification of 28: To a solution of **28** (100 mg, 0.476 mmol) in methanol (2 mL) was added sodium methoxide (51 mg, 0.95 mmol). After 5 min at room temp., TLC analysis indicated complete reversion of **28** to **16**.

X-ray Crystallographic Study of Compound 4: Crystal data: molecular formula: $C_{20}H_{19}O_4N$, molecular mass: 337.4, temperature: 295 K; crystal system: monoclinic; space group: $P2_1/c$; unit cell dimensions: *a* = 7.155(4) Å, *b* = 13.394(4) Å, *c* = 18.649(5) Å, β = 100.21(3)°, volume: 1759(1) $Å^3$; *Z* = 4; density (calculated): 1.27 $g{\cdot}cm^{-3}$; absorption coefficient: 0.8 cm^{-1}. Diffractometer: Enraf−Nonius CAD4; radiation: Mo-K_α; wavelength: 0.71069 Å; θ range for data collection 1−25°; no. of reflections collected: 3521; no. of independent reflections: 3091 [*R*(int) = 0.04]; final *R* indices: *R* = 0.0490, *Rw* = 0.0617; $\Delta\rho_{min}$ = − 0.16 $eÅ^{-3}$, $\Delta\rho_{max}$ = 0.16 $eÅ^{-3}$. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre under the depository no. CCDC-142407. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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