JOC*Article*

Tandem Enantioselective Conjugate Addition−Cyclopropanation. Application to Natural Products Synthesis

Alexandre Alexakis* and Sébastien March

Department of Organic Chemistry, University of Geneva, 30 quai Ernest-Ansermet, Geneva 4, Switzerland CH-1211

alexandre.alexakis@chiorg.unige.ch

Received July 30, 2002

A tandem asymmetric conjugate addition−cyclopropanation was developed, in which a cyclic or linear enone was converted to a TMS-protected 3-substituted-cyclopropanol in an efficient one-pot reaction. These compounds were then selectively cleaved to yield α-methyl-*β*-alkyl ketones, α-methylene-enones, or chain extended *γ*-alkyl-enones. This methodology was applied to the formal total synthesis of (−)-(*S*,*S*)-clavukerin A and (+)-(*R*,*S*)-isoclavukerin.

Introduction

Asymmetric carbon−carbon bond formation is still a challenge in catalysis. Recent years have seen tremendous advances in the 1,4-addition of organometallic reagents to α,*β*-unsaturated ketones.[1] We and others have developed procedures for the use of catalytic copper salts and chiral ligands (such as those illustrated in Figure 1) with organozinc reagents, to give conjugate addition products in good yield and ee.[2]

The nucleophilicity of the intermediate zinc enolate is of interest. Noyori showed that aldehydes react with these enolates,[3] and we demonstrated that the reaction could be extended to chiral acetals in the presence of a Lewis acid such as $BF_3{\cdot}OEt_2$.[4]

In this paper, we report the use of the double bond of this zinc enolate as a starting point for cyclopropanation. The general conjugate addition conditions developed by our group[5] could be exploited to afford the desired zinc−enolate substrate. A small modification was that 3 equiv of diorganozinc reagent were used instead of the usual ratio of 1.3. Thus, the only additional reactant needed to afford the cyclopropanation was diiodomethane. Since the cyclopropanol is known to be unstable,[6] the possibility of in situ silylation was examined. Conditions were found that efficiently lead to enantiomerically pure or highly enriched protected cyclopropanols in a single pot (Scheme 1).

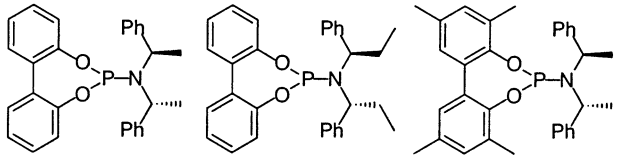


FIGURE 1. Ligands used for the conjugate addition.

The cyclopropane rings were then selectively cleaved in different ways (see Scheme 2). If the cleavage was induced by a Lewis acid, an α-methyl-*β*-alkyl ketone was cleanly obtained. Bromination followed by a dehydrobromination step afforded selectively an α-methylene-*β*-alkyl ketone. Radical-induced opening of the cyclopropane ring led efficiently to a *γ*-alkyl expanded chain enone. In all these opening reactions, the optical purity of the alkyl group remained unchanged, allowing the products to be used as valuable and easily accessible chiral building blocks.

Results and Discussion

Preparation of Protected Cyclopropanols. Preliminary experiments following Saegusa's procedure[7] showed that cyclopropanation was best achieved in

(1) For recent reviews see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem*. **2002**, 3221. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Tomioka, K.; Nagaoka, Y. In *Comprensive Asymmetric Catalysis I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; p 1105.

(2) (a) Alexakis, A. *Pure Appl. Chem*. **2002**, *74*, 37. (b) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779. (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. (d) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375. (e) Yan, M.; Zhou, Z.-Y.; Chan, A. S. C. *Chem. Commun*. **2000**, 115. (f) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879. (g) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (h) Bennett, S. M. W.; Brown, S. M.; Cunningham, A.; Dennis, M. R.; Muxworthy, J. P.; Oakley, M. A.; Woodward, S. *Tetrahedron* **2000**, *56*, 2847. (i) Alexakis, A.; Benhaim, C.; Fournioux, X.; Van der Heuvel, A.; Levêque, J.-M.; March, S.; Rosset, S. *Synlett* **1999**, 1811. (j) Bennett, S. M. W.; Brown, S. M.; Conole, G.; Dennis, M. R.; Fraser, P. K.; Radojevic, S.; McPartlin, M.; Topping, C. M.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3127. (k) Bennett, S. M. W.; Brown, S. M.; Muxworthy, J. P.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 1767. (l) Reetz, M. T. *Pure Appl. Chem*. **1999**, *71*, 1503. (m) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed*. **1999**, *38*, 3518. (n) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429. (o) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed*. **1997**, *36*, 2620.

(3) (a) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 999. (b) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett*. **1996**, *37*, 5141.

(4) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358.

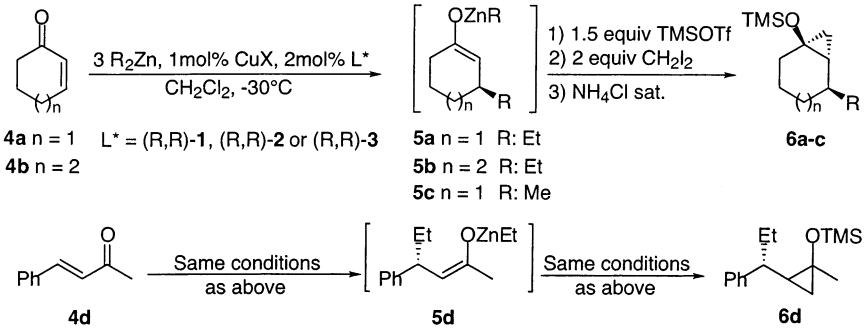
(5) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc*. **2002**, *124*, 5262.

(6) (a) Gibson, D. H.; DePuy, C. H. *Chem. Rev*. **1974**, *74*, 605. (b) DePuy, C. H. *Acc. Chem. Res*. **1968**, *1*, 33.

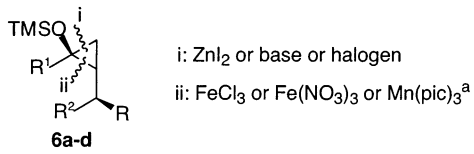
(7) (a) Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Org. Synth*. **1980**, *59*, 113. (b) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem*. **1976**, *41*, 2073.

10.1021/jo026262w CCC: $22.00
Published on Web 11/16/2002

SCHEME 1. Tandem Asymmetric Conjugate Addition−Cyclopropanation



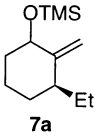
SCHEME 2. Selective Opening of the Cyclopropane Ring



[a] $Mn(pic)_3$: manganese(III) pyridine-2-carboxylate.

dichloromethane rather than in ether or toluene although the chemical yields were in all cases low. There are two different ways to obtain the silylated cyclopropanol, either the zinc enolate can be submitted to cyclopropanation and then silylated or the zinc enolate can be first silylated then cyclopropanated.

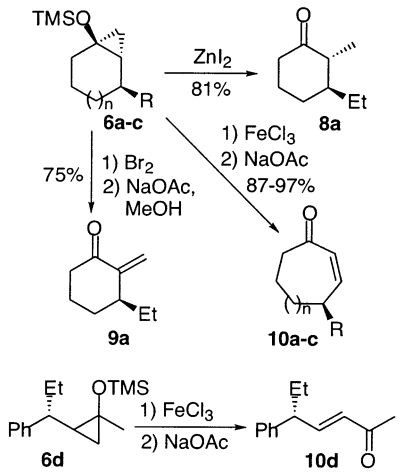
The first attempts of direct cyclopropanation on the zinc enolate **5a** followed by silylation were disappointing. The reaction was not reproducible and once led to the desired compound **6a**, but another case gave the rearranged derivative **7a**.



This isomerization has already been reported in the literature during the course of a Simmons−Smith reaction on the silyl enol ether of cyclohexanone.[8] It is believed to be induced by the zinc(II) iodide formed as the reaction proceeds, and is dependent on the concentration. The authors found that the amount of this unexpected derivative increased as the proportion of the solvent was decreased. However, any attempt to reproduce this rearrangement from our silylated cyclopropanol **6a** failed and only gave the corresponding α-methyl-*β*-ethyl ketone **8a** (see Scheme 3) with complete conversion. Since the direct cyclopropanation of the zinc enolate was not satisfying, we focused on another route.

During his sequence, which led to a ring expansion, Saegusa reported a cyclopropanation of a cyclic silyl enol ether.[7] We decided to change the order of our sequence and proceed to the silylation step directly after the conjugate addition (Scheme 1). With this modification, the cyclopropanation would take place on the more stable silicon enolate. However, we wanted to keep this reaction

SCHEME 3. Opening of the Cyclopropane Ring



in a single vessel, hence we needed to find conditions for the silylation which were compatible with the excess of diorganozinc used. In practice, the transformation of the zinc enolate was very efficiently achieved with 1.5 equiv of TMSOTf at room temperature.[9] This reagent led to a very efficient silylation of the conjugated adduct and did not react at all with the excess of zinc reagent. The formed silyl enol ether was then submitted to the cyclopropanation conditions by simply adding 2 equiv of diiodomethane. This part of the reaction proved to be sensitive to the concentration. It did not take place if the reaction mixture was too diluted and the optimum conditions were found to be 1 mL of dichloromethane for 1 mmol of substrate.

When these conditions were met, we were delighted to isolate the desired protected cyclopropanol **6a** with excellent yield (95%) and enantiomeric excess (98%) in a one-pot procedure with cyclohexenone as starting material (Table 1, entry 1).

This methodology has been extended, without difficulty, to cycloheptenone as well as benzalacetone, an acyclic enone (entries 2 and 4). The face selectivity of the cyclopropanation was high (de 60−84%), although not perfect. The approach of the carbenoid reagent probably occurs from the less hindered face, trans to the R-substituent. In the case of the acyclic benzalacetone, only two diastereoisomers among the 4 theoretical (two for each *E* or *Z* silyl enol ether) were formed, as an inseparable mixture. Purification by column chromatography with silica was not necessary since the crude mixture did

(8) (a) Ryu, I.; Murai, S.; Otani, S.; Sonoda, N. *Tetrahedron Lett.* **1977**, *23*, 1995. (b) Murai, S.; Aya, T.; Renge, T.; Ryu, I.; Sonoda, N. *J. Org. Chem.* **1974**, *39*, 858.

(9) Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 0000.

TABLE 1. Tandem Conjugate Addition−Cyclopropanation

entry	prod	L*	CuX	yield,[a] %	ee,[b] %	de,[c] %
1	**6a**	**2**	CuTC[d]	95	98 *S*	77
2	**6b**	**1**	CuTC[d]	97	93 *S*	84
3	**6c**	**2**	$Cu(OTf)_2$	91	97 *S*	71
4	**6d**	**3**	$Cu(OAc)_2 \cdot H_2O$	97	89 *R*	60

[a] Isolated yield after chromatographic purification. [b] Determined by chiral GC on a quenched aliquot of **5**. The absolute stereochemistry corresponds to the conjugated adduct. [c] Determined by ^{13}C NMR on an average of three carbons. [d] CuTC: copper(I) thiophene-2-carboxylate.

TABLE 2. Opening of the Cyclopropane Ring

entry	prod	conditions[a]	yield,[b] %	ee,[c] %
5	**8a**	A	81	97
6	**9a**	B	55 (75)	97
7	**10a**	C	79	97
8	**10b**	C	79	92
9	**10c**	C	90	96
10	**10d**	C	41 (61)	87[d]

[a] Condition A: ZnI_2. Condition B: (i) Br_2, (ii) NaOAc, MeOH. Condition C: (i) $FeCl_3$, (ii) NaOAc, MeOH. [b] Isolated yield after chromatographic purification, crude ^1H NMR yield in parentheses. [c] Determined by chiral GC. [d] Determined by chiral SFC.

not contain any other byproducts. This mixture of diastereomers was not detrimental to the next planned transformations, as these stereocenters will disappear (see Scheme 3).

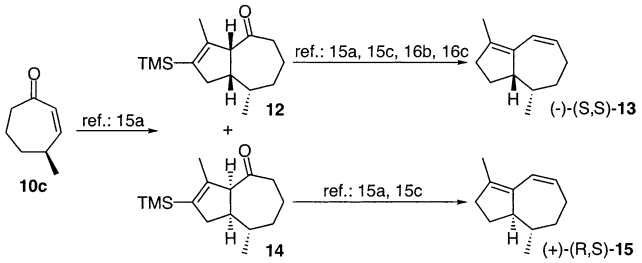
Yields for these reactions ranged from 95% to 97% and enantiomeric excesses were only slightly lower than those obtained in the classical conjugate addition conditions.[5] This may be due either to a concentration or to a solvent effect. As mentioned earlier, our reaction was performed in dichloromethane rather than in ether or toluene and in a much more concentrated medium than the typical procedure for the conjugate addition.

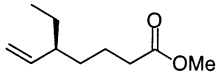
Cleavage of the Cyclopropane Ring. Having these valuable compounds in hand, several opening reactions of the cyclopropane ring were considered (Scheme 2). The first was a selective cleavage of the bond "i" induced by a stoichiometric amount of a Lewis acid, such as ZnI_2,[8] in ether at room temperature (Scheme 3).

The use of a low boiling point solvent was crucial since the α-methyl-β-ethyl ketone **8a** formed, despite its relatively high boiling point, appeared to be very volatile. The reaction was quantitative and very selective, and no racemization was observed. Once the solvent had been carefully removed, the desired ketone **8a** could be obtained in 81% isolated yield[10] (Table 2).

A second method, which also cleaves the bond "i", was taken under consideration. In this case, the reaction was induced by free bromine.[11] The use of an exact stoichiometry and low temperature were found to be necessary to avoid multiple bromination. First attempts to isolate the resulting β-bromo ketone failed or resulted in very low yields. Therefore, the dehydrobromination was carried out directly on the crude mixture with a saturated solution of sodium acetate in methanol at room temperature. Again, special care had to be taken to avoid the loss of material by evaporation. The desired α-methylene-β-ethyl ketone **9a** was obtained in 75% yield, again without any racemization. It was also important not to extend the reaction time for the elimination of HBr since methanol reacted slowly with the reactive Michael acceptor which had formed, to give the linear methyl ester (*S*)-**11a**.[12]

SCHEME 4. Enantioselective Formal Total Synthesis of (−)-(*S,S*)-Clavukerin A and (+)-(*R,S*)-Isoclavukerin





(S)-**11a**

The last method of opening the cyclopropane ring selectively cleaves the bond "ii". It was inspired by the sequence of Saegusa, which led to a ring-expanded enone after elimination of an intermediate β-chloro ketone.[7] Applying this ring-opening reaction to our cyclopropanol bearing a β-alkyl group gave access to the unusual γ-functionalized enone in a stereoselective manner.

Thus, the three cyclic cyclopropanols gave the corresponding ring-expanded enones in good yields and without loss of enantiomeric excess. As expected, cleavage of **6d** occurred exclusively via the more stable secondary radical to give the extended chain enone **10d** after elimination of HCl from the intermediate β-chloro ketone. Only trans olefin was formed, as judged by the coupling constant between the two vinylic protons ($J = 16.1$ Hz). Again, no racemization was observed but the yields were slightly lower compared to the cyclic cyclopropanols.

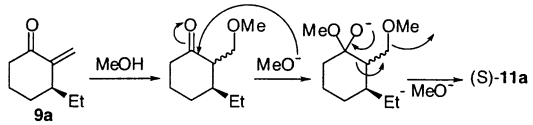
Formal Synthesis of (−)-(*S,S*)-Clavukerin A and (+)-(*R,S*)-Isoclavukerin. This methodology was successfully applied to the asymmetric formal total synthesis of (−)-(*S,S*)-clavukerin A (**13**) and of (+)-(*R,S*)-isoclavukerin (**15**). These sesquiterpenes were isolated from the Okinawan soft coral *Clavularia koellikeri*[13] (Scheme 4).

So far, four syntheses of **15**[14,15] and six of **13**[15,16] have been described, including four enantiocontrolled routes. In all of them, the asymmetric centers were introduced

(10) The missing material is certainly due to unavoidable loss during evaporation.

(11) Murai, S.; Seki, Y.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1974**, *24*, 1032.

(12) The formation of (*S*)-**11a** may be explained by the following mechanism:



(13) For the isolation and absolute configuration determination of clavukerin A, see: Kobayashi, M.; Son, B. W.; Kido, M.; Kyogoku, Y.; Kitawaga, I. *Chem. Pharm. Bull.* **1983**, *31*, 2160. For the absolute configuration determination of isoclavukerin, see: Kusumi, T.; Hamada, T.; Hara, M.; Ishitsuka, M. O.; Ginda, H.; Kakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2019.

(14) Trost, B. M.; Higuchi, R. I. *J. Am. Chem. Soc.* **1996**, *118*, 10094.

through the chiral pool or through kinetic resolution. We herein report the first synthesis where the chirality of **13** and **15** is introduced via a catalytic reaction.

To perform this synthesis, the only modification compared to **10a** was the use of dimethylzinc instead of its ethyl derivative. Such a small change had, however, a large impact on the cyclopropanol formation. When the previous conditions were used (initial excess of dialkylzinc), only incomplete reaction was obtained. This can be ascribed to the lower reactivity of Me_2Zn with CH_2I_2. It was necessary to use only 1.3 equiv of Me_2Zn for the conjugate addition, then proceed to the silylation as previously described and finally to the cyclopropanation with 1.3 equiv of the more reactive diethylzinc. With these new conditions, the methyl-cyclopropanol **6c** was isolated in 91% yield and 97% enantiomeric excess (see Table 1, entry 3). The radical cleavage induced by $FeCl_3$ followed by the elimination of the corresponding β-chloro ketone led to the expected γ-methyl-enone **10c** in very good yield (90%). The elaboration of (±)-clavukerin A and (±)-isoclavukerin from racemic **10c** has been reported earlier[15a] and therefore a formal asymmetric synthesis of these two natural products has been achieved.

Conclusion

A very efficient asymmetric one-pot synthesis of cyclic and linear silylated cyclopropanols has been reported. Three different cleavages of the cyclopropane ring were applied leading to optically pure α-methyl-β-ethyl ketones, α-methylene-β-ethyl ketones, or γ-alkyl-enones. Finally, this last methodology has successfully been applied to the asymmetric formal total synthesis of the trinorguaiane sesquiterpenes (−)-(*S*,*S*)-clavukerin A and (+)-(*R*,*S*)-isoclavukerin.

Experimental Section

Materials. Unless otherwise stated, reagents were obtained commercially and were used without further purification. Cycloheptenone was prepared according to the literature procedure.[17]

General Procedures. CH_2Cl_2, DMF, and Et_3N were distilled from CaH_2; diethyl ether was distilled from sodium benzophenone ketyl. ^1H (300, 400, and 500 MHz) and ^{13}C NMR (75, 100, and 125 MHz) spectra were recorded in $CDCl_3$, and chemical shift (δ) are given in ppm relative to $CHCl_3$. The high-resolution mass spectra (HRMS) were recorded in the EI (70 eV) mode. Optical rotations were measured at 20 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excesses were determined by chiral-GC (capillary column, 10 psi H_2) or chiral-SFC with the stated column. Temperature programs are described as follows: initial temperature (°C)−initial time (min)−temperature gradient (°C/min)−final temperature (°C)−final time (min)−retention times (R_T) are given in min. Flash column chromatography was performed with silica gel 32−63 mm, 60 Å, F_{254}. All reactions were conducted under a nitrogen atmosphere.

General Procedure for the Conjugate Addition−Cyclopropanation. Dry CH_2Cl_2 (10 mL) was added to a dry round-bottom flask containing the copper salt (0.1 mmol) and the chiral ligand (0.2 mmol). This mixture was stirred for 15 min at room temperature and was then cooled to −30 °C. After 15 min, the diethylzinc solution (0.8 M in hexane, 37.5 mL, 30 mmol) was added, followed 20 min later by the enone (10 mmol). The solution was stirred under these conditions until complete consumption of the starting material. An analytical sample of **5** was hydrolyzed and taken for ee determination. TMSOTf (2.2 mL, 12 mmol) neutralized with 0.1 mL of Et_2Zn solution was then added and the reaction mixture was allowed to warm to room temperature. Complete silylation was generally observed in 3−4 h reaction time. Diiodomethane (1.6 mL, 20 mmol) was then added and the reaction mixture was refluxed overnight. It was then cooled to room temperature and hydrolyzed with a saturated solution of NH_4Cl. The organic layer was washed with saturated NH_4Cl then brine, dried with anhyd Na_2CO_3, filtered, and concentrated in vacuo. The products were purified by flash column chromatography (pentane then pentane/Et_2O 9/1) to afford the silylated cyclopropanols as colorless liquids.

(+)-(5(*S*)-Ethylbicyclo[4.1.0]hept-1-yloxy)trimethylsilane (6a): ^1H NMR (400 MHz, $CDCl_3$) δ 2.17 (d, J = 12.9 Hz, 1H), 1.80 (td, J_t = 12.5 Hz, J_d = 5.4 Hz, 1H), 1.60 (m, 2H), 1.46 (m, 3H), 1.22 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H), 0.85 (m, 2H,), 0.29 (t, J = 3.9 Hz, 1H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.2, 40.0, 32.0, 31.0, 29.7, 24.6, 21.2, 18.9, 11.9, 1.4. IR ($CHCl_3$) ν 2999, 2961, 2932, 2858 cm^{-1}. HRMS m/z M$^{+\bullet}$ calcd for $C_{12}H_{24}OSi$ 212.1596, found 212.1590. $[\alpha]^{20}_D$ +18.3 (c 1.0, $CHCl_3$) (determined on the cis/trans ratio). Ee of 98% for hydrolyzed **5a** was measured with a Lipodex E column (program 60-30-15-170-0). R_T = 24.7 (*R*), 27.6 (*S*) min.

(+)-(6(*S*)-Ethylbicyclo[5.1.0]oct-1-yloxy)trimethylsilane (6b): ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (dd, J = 14.6, 6.6 Hz, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.59 (m, 2H), 1.39 (m, 3H), 1,18 (m, 2H), 1.02 (m, 1H), 0.92 (t, J = 7.6 Hz, 3H), 0.69 (m, 2H), 0.34 (t, J = 5.5 Hz, 1H), 0.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.6, 45.6, 38.1, 35.6, 31.3, 30.5, 30.1, 25.1, 24.1, 12.1, 1.4. IR ($CHCl_3$) ν 2994, 2961, 2927, 2875 cm^{-1}. HRMS m/z M$^{+\bullet}$ calcd for $C_{13}H_{26}OSi$ 226.1753, found 226.1757. $[\alpha]^{20}_D$ +34.7 (c 1.2, $CHCl_3$) (determined on the cis/trans ratio). Ee of 93% for hydrolyzed **5b** was measured with a Lipodex E column (program: 50-90-15-170-0). R_T = 92.2 (*S*), 92.8 (*R*) min.

(−)-[1-Methyl-2-(1(*R*)-phenylpropyl)cyclopropoxy]trimethylsilane (6d): ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 5H), 2.31 (m, 1H), 1.74 (m, 2H), 1.43 (s, 2.4H), 1.29 (s, 0.6H), 0.86 (t, J = 7.5 Hz, 3H), 0.77 (m, 1H), 0.69 (m, 0.2H), 0.51 (m, 1H), 0.30 (t, J = 5.9 Hz, 0.8H), 0.18 (s, 7.2H), 0.11 (s, 1.8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ major diastereoisomer: 146.7, 128.1, 127.9, 125.6, 57.6, 45.9, 30.4, 30.0, 26.7, 19.1, 12.1, 1.3. ^{13}C NMR (100 MHz, $CDCl_3$) δ minor diastereoisomer: 146.3, 127.9, 127.8, 125.4, 56.6, 46.0, 30.4, 29.1, 26.4, 19.6, 12.1, 1.3. IR ($CHCl_3$) ν 3065, 3009, 2962, 2930, 2874 cm^{-1}. MS (EI) 247 (1), 233 (1), 159 (5), 143 (100), 117 (10), 91 (12), 73 (91). $[\alpha]^{20}_D$ −57.7 (c 1.07, $CHCl_3$) (determined on the mixture of two diastereoisomers). Ee of 89% for hydrolyzed **5d** was measured with a Lipodex E column (program: 60-50-1-70-0). R_T = 63.5 (*S*), 63.7 (*R*) min.

(+)-(5(*S*)-Methylbicyclo[4.1.0]hept-1-yloxy)trimethylsilane (6c). Dry CH_2Cl_2 (10 mL) was added to a dry round-bottom flask containing copper(II) triflate (36 mg, 0.1 mmol) and ligand (*R*,*R*)-**2** (94 mg, 0.2 mmol). This mixture was stirred for 15 min at room temperature and was then cooled to 0 °C. Dimethylzinc solution (2 M in toluene, 6.5 mL, 13 mmol) was added 15 min later, followed 20 min later by 2-cyclohexenone (0.97 mL, 10 mmol). The solution was stirred under these conditions until complete consumption of the starting material. An analytical sample of **5c** was hydrolyzed and taken for ee determination and TMSOTf (2.2 mL, 12 mmol) neutralized with 0.1 mL of Et_2Zn solution was then added. The reaction mixture was stirred overnight at room temperature and diethylzinc (0.8 M in hexane, 16 mL, 13 mmol) followed by diiodomethane (1.6 mL, 20 mmol) were then added. This solution was refluxed for 3.5 h, cooled to room temperature, and hydrolyzed with a saturated solution of NH_4Cl. The organic layer was washed with saturated NH_4Cl then brine, dried with anhyd Na_2CO_3, filtered, and concentrated in vacuo. The product was purified by flash column chromatog-

(15) (a) Friese, J. C.; Krause, S.; Schäfer, H. J. *Tetrahedron Lett.* **2002**, *43*, 2683. (b) Shimizu, I.; Ishikawa, T. *Tetrahedron Lett.* **1994**, *35*, 1905. (c) Asaoka, M.; Kosaka, T.; Itahana, H.; Takei, H. *Chem. Lett.* **1991**, 1295.

(16) (a) Lee. E.; Yoon, C. H. *Tetrahedron Lett.* **1996**, *37*, 5929. (b) Honda, T.; Ishige, H.; Nagase, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3305. (c) Kim, S. K.; Pak, C. S. *J. Org. Chem.* **1991**, *56*, 6829.

(17) Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109.

raphy (pentane then pentane/Et_2O 9/1), to afford compound **6c** as a colorless liquid (91% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (dt, J = 13.4, 3.7 Hz, 1H), 1.79 (m, 1H), 1.60 (m, 1H), 1.46 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H), 0.84 (m, 4H), 0.30 (t, J = 5.0 Hz, 1H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.4, 32.8, 32.0, 31.9, 26.1, 23.7, 21.3, 18.9, 1.4. IR ($CHCl_3$) ν 2999, 2957, 2869 cm^{-1}. HRMS m/z $M^{+\bullet}$ calcd for $C_{11}H_{22}OSi$ 198.1440, found 198.1438. $[\alpha]^{20}_D$ +22.4 (c 1.04, $CHCl_3$) (determined on the cis/trans ratio). Ee of 97% for hydrolyzed **5c** was measured with a Chiraldex B-TA column (program: 60-0-1-80-10). R_T = 17.6 (R), 18.2 (S) min.

(+)-3(*S*)-Ethyl-2(*R*)-methylcyclohexanone[18] **(8a).** Dry Et_2O (1.4 mL) was added to a dry round-bottom flask containing anhyd ZnI_2 (638 mg, 2 mmol) at room temperature. Silylated cyclopropanol **6a** (425 mg, 2 mmol) was then added and the reaction mixture was stirred for 20 h in these conditions. This mixture was diluted with Et_2O and water and the organic layer was dried with anhyd Na_2CO_3. Careful evaporation of the solvent and purification by flash chromatography (pentane/Et_2O 9/1) gave compound **8a** (226 mg, 1.6 mmol, 81%) as a colorless liquid.^1H NMR (500 MHz, $CDCl_3$) δ 2.38 (m, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.62 (m, 2H), 1.36 (m, 3H), 1.02 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ major diastereoisomer: 213.8, 49.5, 46.7, 41.5, 29.7, 26.2, 25.9, 11.8, 10.2. ^3C NMR (125 MHz, $CDCl_3$) δ minor diastereoisomer: 214.8, 48.8, 43.9, 39.7, 26.5, 23.9, 21.9, 11.6, 11.3. IR ($CHCl_3$) ν 2941, 2870, 1702 cm^{-1}. HRMS m/z $M^{+\bullet}$ calcd for $C_9H_{16}O$ 140.1201, found 140.1204. $[\alpha]^{20}_D$ +23.0 (c 1.02, $CHCl_3$). Ee of 97% for **8a** was measured with a Hydrodex B-3P column (program: 70-40-15-170-5). R_T = 32.3 (2S, 3R), 33.7 (2R, 3S) min.

(+)-3(*S*)-Ethyl-2-methylenecyclohexanone[19] **(9a).** A solution of cyclopropanol **6a** (425 mg, 2 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −78 °C. Bromine (100 μL, 2 mmol) in solution in dry CH_2Cl_2 (1 mL) was added drop by drop over 10 min. Solid sodium pyrosulfite was added 5 h later followed by 6 mL of a saturated solution of sodium acetate in methanol. The reaction was then allowed to warm to room temperature and was stirred overnight. This mixture was diluted with Et_2O and water and the organic layer was dried with anhyd Na_2CO_3. Careful evaporation of the solvent yielded crude compound **9a** (343 mg, 75%) as a pale yellow liquid. ^1H and ^{13}C NMR revealed a good purity. Purification by flash chromatography (pentane/Et_2O 9/1) gave pure compound **9a** in 55% yield as a colorless liquid.^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 5.09 (s, 1H), 2.42 (t, J = 6.6 Hz, 3H), 1.93 (m, 2H), 1.79 (m, 1H), 1.45 (m, 3H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 149.9, 118.9, 43.3, 40.6, 28.9, 26.1, 20.9, 11.3. IR ($CHCl_3$) ν 3009, 2938, 1688 cm^{-1}. HRMS m/z $M^{+\bullet}$ calcd for $C_9H_{14}O$ 138.1045, found 138.1049. $[\alpha]^{20}_D$ +49.2 (c 1.0, $CHCl_3$). Ee of 97% for **9a** was measured with a Hydrodex B-3P column (program: 70-50-15-170-5). R_T = 32.1 (R), 33.6 (S) min.

General Procedure for the Ring Homologation/Chain Extension Reactions. Commercial anhydrous $FeCl_3$ (1.43 g, 8.8 mmol) was further dried in vacuo for 0.5 h in a round-bottom flask. Dry DMF (2.8 mL) was rapidly added at 0 °C, and the brown suspension was stirred at room temperature until clear (dissolution may be enhanced by ultrasonic irradiation). Dry Et_3N (0.56 mL, 4 mmol) was then added and neat cyclopropanol **6a**−**d** (2 mmol) was slowly added via syringe-pump over 1 h at 0 °C. The solution was stirred under these conditions until complete consumption of the starting material and was quenched with saturated NH_4Cl. The mixture was diluted with Et_2O and water and the organic layer was washed with saturated NH_4Cl and $NaHCO_3$. Drying with anhydrous Na_2CO_3 and evaporation in vacuo yielded the crude β-chloro ketone. This nearly colorless liquid was then diluted in 3 mL of a saturated solution of anhydrous sodium acetate in methanol and refluxed for 5 h. Aqueous NH_4Cl and Et_2O were added and the organic layer was washed twice with saturated NH_4Cl. Careful removal of the solvent in vacuo and purification by flash chromatography (pentane/Et_2O 9/1) gave pure γ-alkyl-enones **10a**−**d** as colorless liquids.

(+)-4(*S*)-Ethylcyclohept-2-enone (10a): ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (dd, J = 12.3, 4.1 Hz, 1H), 5.96 (dd, J = 12.2, 2.4 Hz, 1H), 2.58 (m, 2H), 2.40 (m, 1H), 1.95 (m, 1H), 1.80 (m, 2H), 1.52 (m, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 150.7, 131.3, 43.3, 41.8, 31.3, 28.9, 20.5, 11.5. IR ($CHCl_3$) ν 3018, 2936, 1660 cm^{-1}. HRMS m/z $M^{+\bullet}$ calcd for $C_9H_{14}O$ 138.1045, found 138.1050. $[\alpha]^{20}_D$ +72.3 (c 1.7, $CHCl_3$). Ee of 97% for **10a** was measured with a Lipodex E column (program: 80-35-15-170-10). R_T = 21.3 (S), 25.9 (R) min.

(+)-4(*S*)-Ethylcyclooct-2-enone (10b): ^1H NMR (500 MHz, $CDCl_3$) δ 6.10 (m, 2H), 2.94 (m, 1H), 2.84 (m, 1H), 2.51 (m, 1H), 1.82 (m, 1H), 1.69 (m, 2H), 1.59 (m, 1H), 1.48 (m, 3H), 1.27 (m, 1H), 0.96 (t, J = 9.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 148.1, 133.6, 42.5, 40.3, 30.5, 30.5, 23.5, 23.1, 12.0. IR ($CHCl_3$) ν 3009, 2926, 1654 cm^{-1}. HRMS m/z $M^{+\bullet}$ calcd for $C_{10}H_{16}O$ 152.1201, found 152.1200. $[\alpha]^{20}_D$ +8.1 (c 0.16, $CHCl_3$). Ee of 92% for **10b** was measured with a Lipodex E column (program: 110-15-15-170-10). R_T = 4.9 (S), 6.9 (R) min.

(−)-4(*S*)-Methylcyclohept-2-enone[20] **(10c):** ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, J = 12.1, 3.8 Hz, 1H), 5.93 (dd, J = 12.1, 1.9 Hz, 1H), 2.60 (m, 3H), 1.95 (m, 1H), 1.81 (m, 2H), 1.52 (m, 1H), 1.17 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 151.6, 130.6, 43.6, 35.7, 34.3, 21.9, 20.6. IR ($CHCl_3$) ν 2964, 2934, 1657 cm^{-1}. HRMS m/z $M^{+\bullet}$ calcd for $C_8H_{12}O$ 124.0888, found 124.0899. $[\alpha]^{20}_D$ −138.4 (c 0.48, $CHCl_3$). Ee of 96% for **10c** was measured with a Hydrodex B-3P column (program: 70-40-15-170-5). R_T = 31.2 (S), 33.8 (R) min.

(−)-5(*R*)-Phenylhept-3-en-2-one (10d): ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.28 (m, 1H), 7.21 (m, 2H), 6.91 (dd, J = 16.1, 7.8 Hz, 1H), 6.09 (d, J = 16.1 Hz, 1H), 3.34 (m, 1H), 2.26 (s, 3H), 1.85 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 150.7, 142.0, 130.3, 128.7 (2), 127.7 (2), 126.8, 50.4, 27.8, 27.0, 12.1. IR ($CHCl_3$) ν 3028, 3012, 2968, 1672 cm^{-1}. HRMS m/z $M^{+\bullet}$ calcd for $C_{13}H_{16}O$ 188.1201, found 188.1192. $[\alpha]^{20}_D$ −10.1 (c 1.0, $CHCl_3$). Ee of 87% for **10d** was measured by chiral SFC with a Chiralcel OD-H column (1% MeOH, flow rate 2 mL/min). R_T = 4.48 (R), 4.88 (S) min.

Acknowledgment. The authors thank the Swiss National Research Foundation No. 20-61891.00 and COST action D12/0022/99 for financial support, and Xavier Rathgeb for his very efficient synthetic help.

Supporting Information Available: ^1H and ^{13}C spectra for compounds **6a**−**d**, **8a**, **9a**, and **10a**−**d** plus Chiral GC for compounds **5a**−**d** (hydrolyzed to the corresponding ketone), **8a**, **9a**, and **10a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026262W

(18) Miller, B.; Matjeka, E. R. *J. Am. Chem. Soc.* **1980**, *102*, 4772.
(19) (a) Tamura, R.; Watabe, K.-I.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 4895. (b) Tamura, R.; Watabe, K.-I.; Katayama, H.; Suzuki, H.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 408.
(20) Heathcock, C. H.; Germroth, T. C.; Graham, S. L. *J. Org. Chem.* **1979**, *44*, 4481.