Headline Articles

Stereoselective Synthesis of Cyclopropanes via Homoallylic Participation

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A facile method for synthesizing *trans*-disubstituted cyclopropanes is described. γ,γ-Dimethyl homoallyl alcohols, upon conversion to the corresponding triflate, undergo smooth cyclization to give cyclopropanes in a stereoselective manner (*trans*) and in a stereospecific manner (inversion of configuration at the chiral center). Various functionalities could be introduced at the α-position of the newly formed cyclopropane ring by treating the cyclization mixture with hetero as well as carbon nucleophiles. Alternatively, treatment of the reaction mixture with triethylamine effects the clean elimination of a triflic acid to give high yields of the cyclopropanes with a 2-propenyl group, which are convertible to the corresponding cyclopropyl methyl ketones by ozonolysis in high yields. Also described is an application of the method to a short-step synthesis of a cyclopropane-containing eicosanoid, related to marine prostanoid biosynthesis.

Cyclopropanes are ubiquitous in natural products, some of which are of biological and medicinal significance.[1,2] The unique bonding structure of this three-membered ring is not only chemically intriguing, but is also mechanistically related to various biological events.[1] Thus, considerable interest is currently focused on the synthesis of cyclopropanes in an enantio- and diastereoselective manner.[3]

We recently established a new efficient method for the stereocontrolled synthesis of difunctional *trans*-cyclopropanes **A** (Fig. 1),[4] a class of structural motif often seen in natural products, particularly in those of the marine origin,[5] such as halicholactone (**1**),[6] constanolactone A (**2**),[7] and an eicosanoid **3**.[8] A related structure with an additional substituent on the cyclopropane ring is also included in an antibiotic, ambruticin (**4**).[9] This paper features a synthetic method for *trans*-disubstituted cyclopropanes,[4a] and also describes its application to a short-step total synthesis of eicosanoid **3**.[4b]

Our interest in this area stemmed from continuing studies on new synthetic methods based on *homoallylic participation*, which is one of the specific examples of neighboring-group participation,[11] and characterizes the reactivity of homoallylic systems in terms of the kinetics as well as stereochemistry (Scheme 1).[10,11] The effect is also relevant to the biosynthetic pathways of some natural products,[2,5] and has also been attracting much interest from the fields of physical and theoretical chemistry ever since classical/nonclassical arguments were presented in the 1960's.[12] However, the synthetic aspects of this effect seem to have been left aside so far, presumably due to the obvious difficulty in controlling the reaction pathway. An illustrative example is

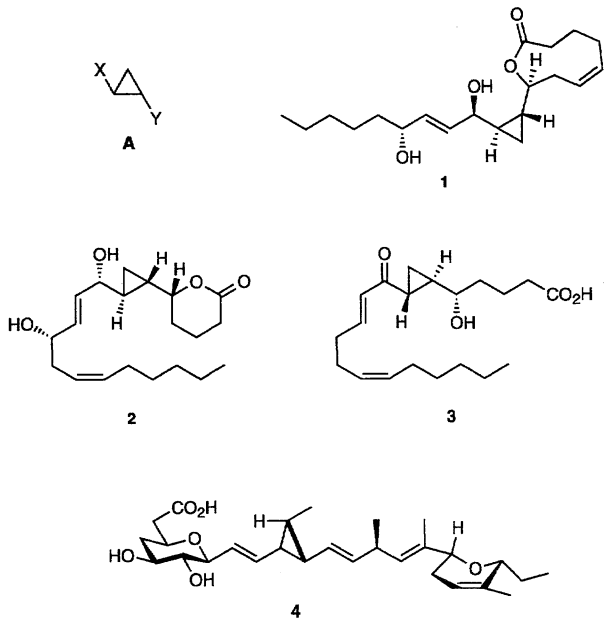


Fig. 1. Natural products containing difunctional *trans*-cyclopropane.

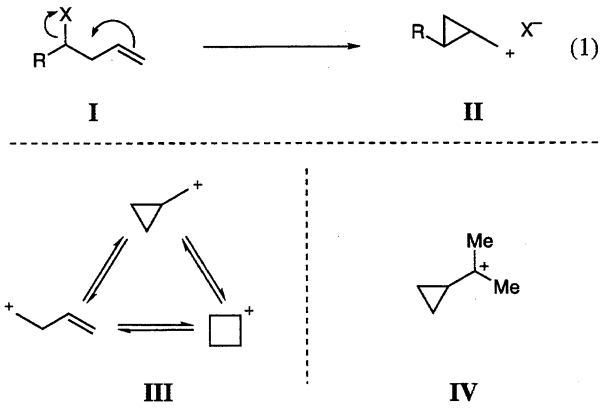
the parent allyl system (R = H, **I** in Eq. 1, Scheme 1), which generates the $C_4H_7^+$ cation triad (see **III** in Scheme 1).[12] In a classical expression, the cations are interconvertible, and the ready skeletal changes often lead to a statistical distribution of multiple products. We envisioned, however, that we would have an opportunity to develop new useful synthetic reactions, provided that we were able to somehow control the participation process.

We reasoned that the installation of two methyl groups at the end of the allyl group would totally alter the situation (see **IV** in Scheme 1).[13] Since the *tertiary* cyclopropylmethyl cation is extremely stabilized, it undergoes selective trapping without any skeletal changes to give a product. Along these lines, a reaction scheme was envisioned based on this idea (Scheme 2). By virtue of the high π-electron density of the trisubstituted olefin, compound **5**, upon suitable activation, would undergo facile homoallylic participation to generate **6**. This species, which is either ionic or covalent in nature, would then undergo selective trapping by a nucleophile to give cyclopropane **7**. Another possible fate of **6** would be a base-induced elimination of HX, thereby giving vinylcyclopropane **8**.

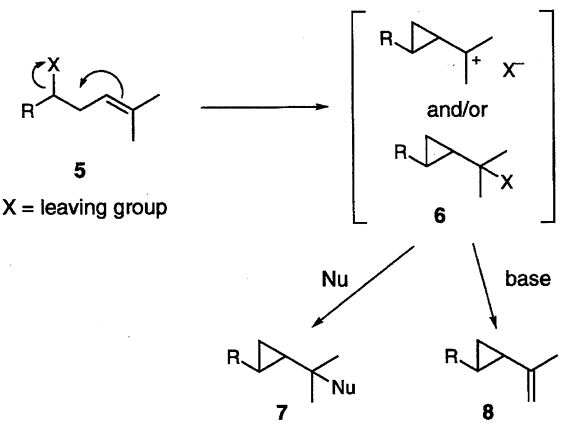
Results and Discussion

The strategy was reduced into practice simply by exploiting a triflate chemistry;[13] some of the characteristic features are outlined below.

Reaction Profile. Upon the treatment of homoallyl alcohol **9**[14] with triflic anhydride and *s*-collidine (CH_2Cl_2, −78 °C), TLC-monitoring showed an immediate consumption of **9** (R_f 0.42; hexane/EtOAc = 4/1) and the appearance of a new single spot (R_f 0.31). Quenching after 15 min with H_2O gave cyclopropylmethyl alcohol **10** in 87% yield as the sole product (Scheme 3). The new spot that appeared upon triflation proved to correspond to alcohol **10**, which could be reasonably assumed to be hydrolysate of **6′**, the likely intermediate after the cyclization.[15,16] Thus, the cyclopropane-formation proved to occur spontaneously without resort to any activators.[13] The disubstituted cyclopropane **10**, thus obtained, was solely composed of the *trans*-isomer (vide infra).



Scheme 1.

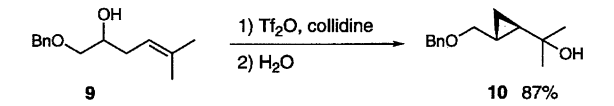


Scheme 2.

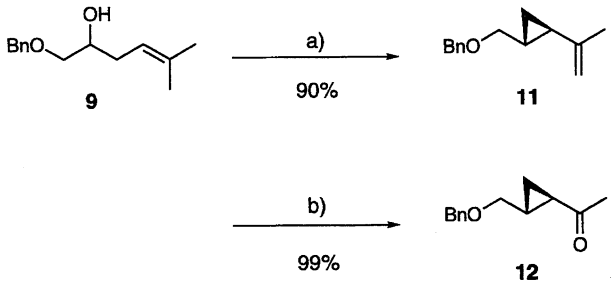
Elimination. By assuming the intermediacy of *t*-triflate **6′**, we reasoned that the elimination of a triflic acid from **6′** would be viable if suitable basic conditions were applied (see Introduction). Indeed, after cyclization was complete, the addition of triethylamine to the reaction mixture effected the clean elimination to give vinylcyclopropane **11** in excellent yield (Scheme 4). The product **11** was again solely composed of the *trans*-isomer (vide infra). Furthermore, we were pleased to find that the ozonolysis of **11** proceeded cleanly, without destroying the cyclopropane ring, to give quantitative yield of cyclopropyl methyl ketone **12**. It is noteworthy that cyclopropane **12** has two versatile functionalities for chain extension towards both directions.

Stereoselectivity. The rigorous *trans*-selectivity of the cyclopropane-forming reaction could be rationalized by the preferred transition state **X** (Fig. 2). In contrast, the other possible transition state **Y**, leading to the *cis*-isomer, is highly disfavored due to the repulsion between the olefinic moiety and the substituent R.

Stereospecificity. Since a super leaving group (TfO^-)



Scheme 3.



Scheme 4. a) Tf_2O, collidine/CH_2Cl_2, −78 °C, 15 min then Et_3N, −78 °C → room temperature, b) O_3/MeOH, −78 °C then Me_2S, −78 °C → room temperature.

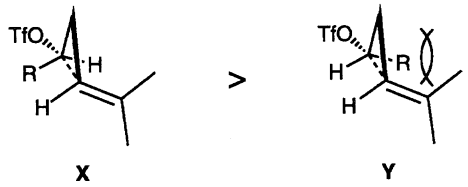


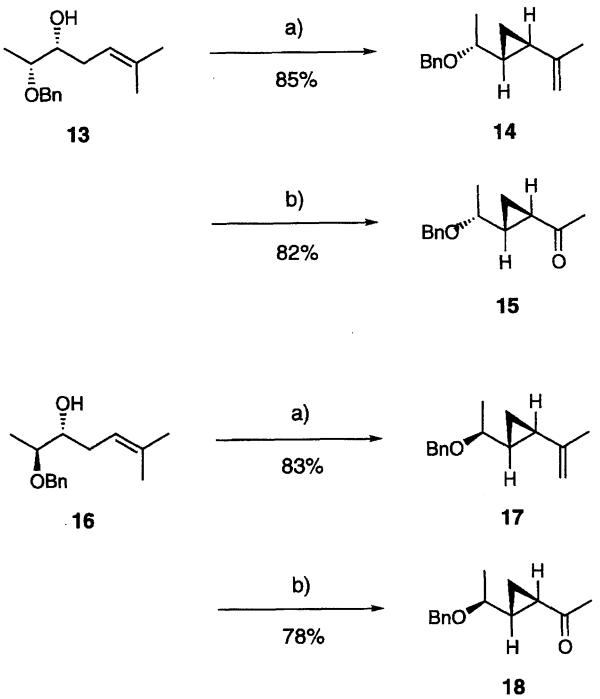
Fig. 2. Transition states of the cyclization.

is employed in the reaction, we were concerned about the loss of stereochemical integrity, i. e. stereo-randomization via an S_N1 process. Notice that the above examples told us nothing, since the starting material **9** is a racemate with a single stereogenic center. However, we were pleased to confirm the clean *inversion* of configuration at the chiral center, as evidenced by the reactions of diastereomeric homoallyl alcohols **13** and **16** (Scheme 5).[17] Vinylcyclopropanes **14** and **17** were obtained in high yields, specifically, from **13** and **16**, respectively. The isomers were carefully subjected to ozonolysis, as before, to give diastereomeric ketones **15** and **18** in high yields, respectively. The configuration of the exocyclic chiral center was clarified by the X-ray analysis of the 2,4-dinitrophenylhydrazone derived from **18**.[18]

The features, stated above, clearly show the promising potential of the method for enantio- and diastereospecific synthesis; a good example will be seen in a short-step synthesis of a marine natural product **3** (vide infra).

Synthesis of Cyclopropanes with Various α-Functionalities. We found that the cyclized triflate **6′** could be trapped in situ by various hetero or carbon nucleophiles, instead of H_2O, to give cyclopropanes with various functionalities at the α-position of the newly formed three-membered ring (Table 1).

The results of the reaction with chalcogenide nucleophiles are listed in Runs 1, 2, and 3. The reaction with methanol (−78 °C→room temperature) gave methyl ether **19** in 81% yield (Run 1). Cyclopropylmethyl sulfide **20** and selenide **21** were obtained in high yields by a reaction with *p*-*t*-butylbenzenethiol (−78→−5 °C) and with diisobutylaluminum benzeneselenolate[19] (−78→−30 °C), respectively (Runs 2 and 3).



Scheme 5. a) Tf_2O, collidine/CH_2Cl_2, −78 °C then Et_3N, −78 °C → room temperature, b) O_3/MeOH, −78 °C then Me_2S, −78 °C → room temperature.

Table 1. Synthesis of Cyclopropanes with Various α-Functionalities

Run	Nucleophiles[a]	Product	Yield/%
1	MeOH	BnO, OMe **19**	81
2	*t*-Bu-SH	BnO, S-*t*-Bu **20**	80
3	$PhSeAl(i\text{-}Bu)_2$	BnO, SePh **21**	82
4	OSiMe$_3$, N, N, OSiMe$_3$	BnO, O, N, NH, O **22**	93
5	Me_3SiN_3	BnO, N_3 **23**	84
6	Me_3Al	BnO, Me **24**	90
7	Et_2AlCN	BnO, CN **25**	61
8	$i\text{-}Bu_3Al$	BnO, H **26**	82

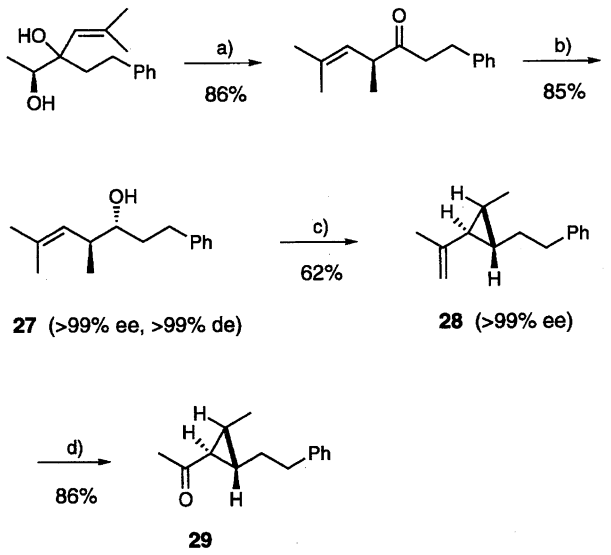
a) Nucleophiles (3 mol amt.) were added after triflation at −78 °C.

In contrast to triethylamine, which induces the elimination reaction, the less-basic nitrogen nucleophiles undergo substitution, thereby introducing nitrogen substituents to the α-position of the cyclopropane. Bis-TMS-uracil[20] cleanly took part in the reaction (−78→−30 °C) to give compound **22** with potential therapeutic interest (Run 4).[21] The regiochemistry of the substitution of the uracil nucleus was determined by an NOE study (see Experimental). Azido group was also introduced using trimethylsilyl azide (−78 °C→room temperature, Run 5).

The reaction examples with carbon nucleophiles for the C–C bond formation are illustrated by the reactions with trimethylaluminum (−78→−30 °C, Run 6) and diethylaluminum cyanide (−78 °C→room temperature, Run 7). In contrast, triisobutylaluminum behaved solely as a β-hydride donor to give the isopropyl-substituted cyclopropane **26** as the only detectable product (−78→−30 °C, Run 8). Unfortunately, some other nucleophiles tested, such as enol silyl ether, ketene silyl acetal or allylsilane, failed to give the substitution product.

All of the cyclopropanes listed in Table 1 are solely composed of the *trans*-isomers, as evidenced by high-field NMR analyses.

Synthesis of Trisubstituted Vinylcyclopropane. A trisubstituted cyclopropane **29**, reminiscent of the subunit



Scheme 6. a) MsCl, Et_3N/CH_2Cl_2, 0 °C, then SiO_2, b) L-Selectride®/THF, −78 °C, c) Tf_2O, collidine/CH_2Cl_2, −78 °C, 30 min then Et_3N, −78 °C →room temperature, d) O_3/MeOH, −78 °C then Me_2S, −78 °C → room temperature.

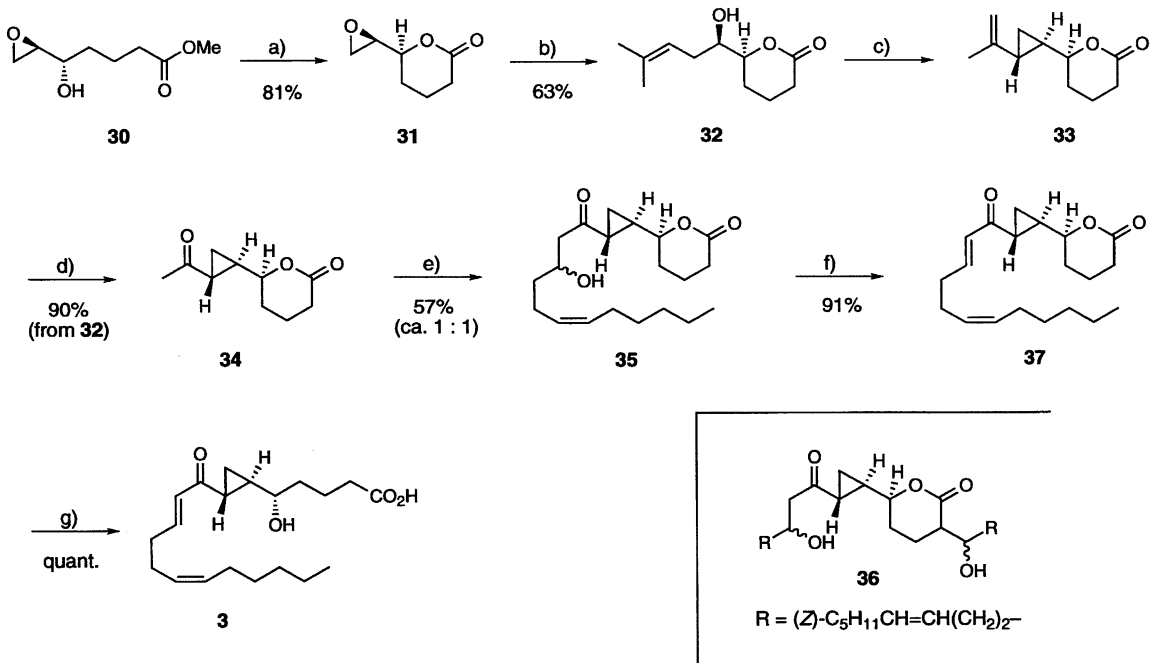
in ambruticin (**4**), was also obtained from the enantiopure homoallyl alcohol **27** as a sole diastereomer (Scheme 6). Stereo-defined alcohol **27** was prepared by a pinacol-type rearrangement and a stereoselective reduction, as reported previously.[22] The cyclopropane formation was accomplished by essentially the same procedure as that stated above, and the ozonolysis also proceeded smoothly. The enantiomeric excess of **28** (>99%) was determined by its chiral GC analysis.

Synthesis of Cyclopropane-Containing Eicosanoid 3. We applied this method to the synthesis of a cyclopropane-containing eicosanoid **3**, a compound related to the marine prostanoid biosynthesis,[5,23] which was isolated from the incubation of arachidonic acid with an acetone powder of the soft coral *Plexaura homomalla*.[8] The relative configuration of **3** was determined by chemical synthesis,[24] while, interestingly, in an absolute sense, **3** was reported to be racemic.

Our synthesis started with the known hydroxy ester **30**, available from 2-deoxy-D-ribose,[25] which was subjected to acidic conditions to give epoxy lactone **31** in 81% yield (Scheme 7). A subsequent introduction of the 2-methyl-1-propenyl moiety turned out to be not straightforward. After considerable experimentation, we chose to use the higher-order cuprate[26] to obtain homoallyl alcohol **32** in good yield.

The key cyclopropane-forming reaction was carried out by the standard procedure. Thus, alcohol **32** was treated with triflic anhydride and *s*-collidine (CH_2Cl_2, −78 °C). The cyclization turned out to be slower than the model reactions, but, nonetheless, proceeded cleanly within 1 h. Then, triethylamine was added to the mixture, and warming to room temperature effected the clean elimination to give vinylcyclopropane **33** as a single product. Since it turned out that cyclopropane **33** is rather unstable, we opted to subject it directly to the ozonolysis to obtain a single cyclopropyl methyl ketone **34** in 90% yield from **32**.

The aldol addition of cyclopropyl methyl ketone **34** to commercially available (*Z*)-4-decenal was carried out by



Scheme 7. a) cat. TsOH/benzene, reflux, 20 min, b) $[(CH_3)_2C{=}CH]_2CuCNLi_2/Et_2O$, −78 →−20 °C, c) Tf_2O, collidine/CH_2Cl_2, −78 °C then Et_3N, −78 °C → room temperature, d) O_3/MeOH, −78 °C then Me_2S, −78 °C → room temperature, e) Bu_2BOTf, *i*-Pr_2NEt/CH_2Cl_2, −78 °C then (*Z*)-$C_5H_{11}CH{=}CH(CH_2)_2CHO$, 1 h, f) MsCl, Et_3N/CH_2Cl_2, 0 °C, 30 min then DBN, 0 °C → room temperature, g) LiOH/THF–H_2O, 0 °C, 10 min.

using the boron enolate[27] to give aldol **35** in 57% yield. The enolization of ketone **34** turned out to be sluggish in comparison with that of usual ketones, and required the use of the reagents in excess. As a result, bis-aldol **36**, derived from the double enolization–addition, was also obtained as the side product in 14% yield as a mixture of diastereomers. We presume that this is due to the reduced acidity of the methyl proton in **34** by the high electron donation to the carbonyl group by the cyclopropyl group.[28]

Subsequent dehydration of aldol **35** was cleanly achieved by mesylation, followed by a treatment with DBN to give lactone **37** in 91% yield. All of the spectroscopic data and the optical rotation of **37** were in agreement with those reported for the chiral material by White et al.[24] Saponification of lactone **37**[24] quantitatively produced the cyclopropane-containing eicosanoid **3**, and the ^{1}H NMR and IR data were again in agreement with the reported data.[24] It was noted that hydroxy carboxylic acid **1** is prone to relactonization to give **37**, as previously reported.[24] The overall yield of the seven-step synthesis was 24% from the known ester **30**.

Conclusion

A simple and stereoselective method for the synthesis of difunctionalized *trans*-cyclopropanes has been developed, which will find wide utilities in the synthesis of natural products armed with these substructures. A short-step synthesis of eicosanoid **3** illustrates the promising potential in this context.

Experimental

General. All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Dichloromethane was successively distilled from P_2O_5 and CaH_2 and stored over molecular sieves 4A. Triflic anhydride was kindly donated by Central Glass Co., and was used as such. For thin-layer chromatography (TLC) analysis, Merck precoated plates (silica gel 60 F_{254}, 1.05715, 0.25 mm) were used Silica gel 60 K070 W (70—230 mesh) of Katayama Chemical was used for column chromatography. Silica-gel preparative TLC was performed on Merck silica gel 60 PF_{254} (7747). ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) were measured on a JEOL JNM EX-400 spectrometer in $CDCl_3$. Infrared (IR) spectra were recorded on a JASCO IRA-202 spectrometer. High-resolution mass spectra under electron impact condition (HRMS) were obtained with a JEOL JMS DX302.

Typical Procedure for the Syntheses of α-Substituted Cyclopropanes Is Described for the Synthesis of Cyclopropylmethanol 10. To a mixture of homoallyl alcohol **9** (117 mg, 0.530 mmol) and *s*-collidine (94.6 mg, 0.781 mmol) in CH_2Cl_2 (7.0 ml) at −78 °C was slowly added a solution of triflic anhydride (224 mg, 0.795 mmol) in CH_2Cl_2 (1.0 ml). After 15 min, sat. $NaHCO_3$ aq solution was added to the reaction mixture. The products were extracted with EtOAc, and the combined extracts were washed with brine and dried (Na_2SO_4). Purification with silica-gel preparative TLC (hexane/EtOAc = 7/3) gave **10** (102 mg, 87%) as colorless oil; ^{1}H NMR δ = 7.33—7.22 (m, 5H), 4.54 (d, 1H, J = 12.5 Hz), 4.49 (d, 1H, J = 12.5 Hz), 3.34 (dd, 1H, J_1 = 9.9, J_2 = 6.6 Hz), 3.30 (dd, 1H, J_1 = 9.9, J_2 = 6.6 Hz), 1.81 (s, 1H), 1.27—1.08 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H), 0.84 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.0 Hz), 0.59 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.0 Hz), 0.35 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.0 Hz); ^{13}C NMR δ = 138.4, 128.2, 127.5, 127.4, 73.8, 72.3, 69.1, 28.8, 28.6, 28.3, 14.5, 6.7; IR (neat) 3450, 2975, 2870, 1750, 1455, 1360, 1230, 1160, 1175, 955, 740, 700 cm^{-1}. HRMS Found: *m/z* 219.1403. Calcd for $C_{14}H_{19}O_2$, $(M-H)^+$, 219.1385.

Methyl Ether 19: The cyclization protocol described for the synthesis of **10** was applied for **9** (108 mg, 0.491 mmol) by using *s*-collidine (90.1 mg, 0.744 mmol) and triflic anhydride (216 mg, 0.766 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, methanol (1.0 ml) was added, and the reaction was warmed to room temperature in 1 h. Purification with silica-gel preparative TLC (hexane/EtOAc = 4/1) gave **19** (93.3 mg, 81%) as colorless oil; ^{1}H NMR δ = 7.34—7.24 (m, 5H), 4.55 (d, 1H, J = 12.2 Hz), 4.50 (d, 1H, J = 12.2 Hz), 3.43 (dd, 1H, J_1 = 10.2, J_2 = 6.3 Hz), 3.27 (dd, 1H, J_1 = 10.2, J_2 = 7.3 Hz), 3.25 (s, 3H), 1.17—1.08 (m, 7H), 0.82 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz), 0.58 (ddd, 1H, J_1 = 8.3, J_2 = J_3 = 5.3 Hz), 0.41 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz); ^{13}C NMR δ = 138.6, 128.3, 127.5 (2C), 74.0, 72.5, 49.6, 25.5, 24.0, 23.7, 14.8, 7.3; IR (neat) 3000, 2850, 1500, 1450, 1360, 1310, 1250, 1200, 1180, 1140, 1100, 1070, 1030, 880, 820, 740, 700 cm^{-1}. HRMS Found: *m/z* 234.1611. Calcd for $C_{15}H_{22}O_2$: M^+, 234.1620.

Sulfide 20: The cyclization protocol described for the synthesis of **10** was applied for **9** (120 mg, 0.545 mmol) by using *s*-collidine (99.5 mg, 0.821 mmol) and triflic anhydride (231 mg, 0.820 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, *p-t*-butylbenzenethiol (182 mg, 1.10 mmol) was added, and the reaction was warmed to −5 °C in 50 min. Purification with silica-gel preparative TLC (hexane/EtOAc = 19/1) gave **20** (160 mg, 80%) as colorless oil; ^{1}H NMR δ = 7.47 (d, 2H, J = 8.6 Hz), 7.35—7.23 (m, 7H), 4.53 (d, 1H, J = 12.2 Hz), 4.49 (d, 1H, J = 12.2 Hz), 3.45 (dd, 1H, J_1 = 10.2, J_2 = 5.9 Hz), 3.17 (dd, 1H, J_1 = 10.2, J_2 = 7.3 Hz), 1.31 (s, 9H), 1.18—1.07 (m, 1H), 1.16 (s, 3H), 1.11 (s, 3H), 0.96 (ddd, 1H, J_1 = 8.6, J_2 = J_3 = 5.3 Hz), 0.60 (ddd, 1H, J_1 = 8.6, J_2 = J_3 = 5.3 Hz), 0.41 (ddd, 1H, J_1 = 8.6, J_2 = J_3 = 5.3 Hz); ^{13}C NMR δ = 151.8, 138.6, 137.3, 128.7, 128.3, 127.6, 127.5, 125.4, 73.9, 72.5, 48.4, 34.6, 31.3, 28.0, 27.2, 26.8, 15.6, 8.0; IR (neat) 2890, 1600, 1500, 1460, 1395, 1370, 1270, 1205, 1120, 1030, 840, 743, 705 cm^{-1}. HRMS Found: *m/z* 368.2143. Calcd for $C_{24}H_{32}O^{32}S$: M^+, 368.2174.

Selenide 21: The cyclization protocol described for the synthesis of **10** was applied for **9** (110 mg, 0.500 mmol) by using *s*-collidine (91.1 mg, 0.750 mmol) and triflic anhydride (211 mg, 0.750 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, diisobutylaluminum benzeneselenolate[19] (1.08 M in CH_2Cl_2, 2.30 ml, 2.48 mmol) (1 M = 1 mol dm^{-3}) was added, and the reaction was warmed to −30 °C in 30 min. Purification with silica-gel preparative TLC (hexane/EtOAc = 19/1) gave **21** (148 mg, 82%) as colorless oil; ^{1}H NMR δ = 7.65 (dd, 2H, J_1 = 6.6, J_2 = 1.7 Hz), 7.37—7.23 (m, 8H), 4.53 (d, 1H, J = 12.2 Hz), 4.48 (d, 1H, J = 12.2 Hz), 3.41 (dd, 1H, J_1 = 10.2, J_2 = 5.9 Hz), 3.17 (dd, 1H, J_1 = 10.2, J_2 = 7.3 Hz), 1.29 (s, 3H), 1.24 (s, 3H), 1.22—1.09 (m, 1H), 1.06 (ddd, 1H, J_1 = 8.6, J_2 = J_3 = 5.3 Hz), 0.63 (ddd, 1H, J_1 = 8.6, J_2 = J_3 = 5.3 Hz), 0.43 (ddd, 1H, J_1 = 8.6, J_2 = J_3 = 5.3 Hz); ^{13}C NMR δ = 138.5, 138.3, 128.5, 128.4, 128.3, 128.0, 127.6, 127.5, 73.8, 72.5, 46.4, 29.0, 28.2, 27.8, 16.1, 8.6; IR (neat) 2860, 1575, 1450, 1360, 1300, 1243, 1200, 1175, 1115, 1020, 740, 700 cm^{-1}. HRMS Found: *m/z* 360.1011. Calcd for $C_{20}H_{24}O^{80}Se$: M^+, 360.0992.

Uracil 22: The cyclization protocol described for the synthesis of **10** was applied for **9** (116 mg, 0.527 mmol) by using *s*-collidine (98.2 mg, 0.810 mmol) and triflic anhydride (224 mg, 0.795 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, bis-TMS-uracil[20] (298 mg, 1.58 mmol) was added, and the reaction was warmed to −30 °C in 40 min. Purification with silica-gel preparative TLC (hexane/EtOAc = 1/1) gave **22** (154 mg, 93%) as colorless crystalline

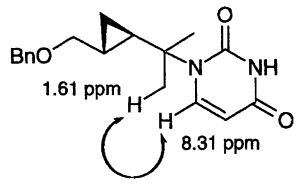


Fig. 3. NOE of **22**.

solid; ^{1}H NMR δ = 9.26 (broad s, 1H), 8.31 (d, 1H, J = 8.2 Hz), 7.40—7.27 (m, 5H), 5.39 (d, 1H, J = 8.2 Hz), 4.54 (d, 1H, J = 11.6 Hz), 4.46 (d, 1H, J = 11.6 Hz), 3.76 (dd, 1H, J_1 = 9.9, J_2 = 5.3 Hz), 3.15 (dd, 1H, J_1 = 9.9, J_2 = 8.2 Hz), 1.61 (s, 3H), 1.42—1.30 (m, 1H), 1.37 (s, 3H), 1.17 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz), 0.73 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz), 0.62 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz); ^{13}C NMR δ = 164.1, 151.3, 143.2, 137.9, 128.5, 127.9, 127.7, 100.6, 73.7, 73.1, 64.0, 28.0, 25.5, 21.9, 16.5, 8.0; IR (KBr) 3000, 2850, 1680, 1450, 1375, 1340, 1307, 1240, 1155, 1095, 1020, 880, 810, 750, 700, 560 cm^{-1}. HRMS Found: *m/z* 314.1612. Calcd for $C_{18}H_{22}N_2O_3$; M^+, 314.1630. The results of the NOE study are shown in Fig. 3.

Azide 23: The cyclization protocol described for the synthesis of **10** was applied for **9** (103 mg, 0.468 mmol) by using *s*-collidine (85.3 mg, 0.704 mmol) and triflic anhydride (199 mg, 0.705 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, trimethylsilyl azide (162 mg, 1.40 mmol) was added, and the reaction was warmed to room temperature in 1 h. Purification with silica-gel preparative TLC (hexane/EtOAc = 19/1) gave **23** (96.5 mg, 84%) as colorless oil; ^{1}H NMR δ = 7.37—7.22 (m, 5H), 4.53 (d, 1H, J = 12.2 Hz), 4.49 (d, 1H, J = 12.2 Hz), 3.38 (dd, 1H, J_1 = 10.2, J_2 = 6.3 Hz), 3.29 (dd, 1H, J_1 = 10.2, J_2 = 6.9 Hz), 1.22—1.13 (m, 7H), 0.89 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz), 0.65 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz), 0.43 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.3 Hz); ^{13}C NMR δ = 138.5, 128.4, 127.5 (2C), 73.3, 72.5, 60.8, 26.7, 25.6, 25.5, 14.6, 6.9; IR (neat) 2950, 2850, 2100, 1500, 1450, 1360, 1200, 1160, 1140, 1100, 1020, 820, 740, 700 cm^{-1}. HRMS Found: *m/z* 245.1505. Calcd for $C_{14}H_{19}N_3O$: M^+, 245.1528.

Cyclopropane 24: The cyclization protocol described for the synthesis of **10** was applied for **9** (103 mg, 0.468 mmol) by using *s*-collidine (83.9 mg, 0.692 mmol) and triflic anhydride (202 mg, 0.716 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, trimethylaluminum (1.04 M in toluene, 1.35 ml, 1.40 mmol) was added, and the reaction was warmed to −30 °C in 30 min. Purification with silica-gel preparative TLC (hexane/EtOAc = 19/1) gave **24** (92.0 mg, 90%) as colorless oil; ^{1}H NMR δ = 7.35—7.22 (m, 5H), 4.52 (s, 2H), 3.40 (dd, 1H, J_1 = 10.2, J_2 = 6.6 Hz), 3.21 (dd, 1H, J_1 = 10.2, J_2 = 7.6 Hz), 1.07—0.86 (m, 1H), 0.84 (s, 9H), 0.61—0.43 (m, 2H), 0.23 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 4.6 Hz); ^{13}C NMR δ = 138.8, 128.3, 127.6, 127.4, 74.7, 72.4, 29.3, 29.0, 28.5, 14.1, 6.6; IR (neat) 2950, 1600, 1450, 1360, 1265, 1200, 1100, 1030, 905, 810, 740, 700 cm^{-1}. HRMS Found: *m/z* 218.1670. Calcd for $C_{15}H_{22}O$: M^+, 218.1671.

Nitrile 25: The cyclization protocol described for the synthesis of **10** was applied for **9** (73.2 mg, 0.333 mmol) by using *s*-collidine (59.8 mg, 0.493 mmol) and triflic anhydride (148 mg, 0.525 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, diethylaluminum cyanide (1.0 M in toluene, 1.0 ml, 1.0 mmol) was added, and the reaction was warmed to room temperature in 1 h. Purification with silica-gel preparative TLC (hexane/EtOAc=4/1) gave **25** (46.8 mg, 61%) as colorless oil; ^{1}H NMR δ = 7.36—7.25 (m, 5H), 4.54 (d, 1H, J = 12.1 Hz), 4.49 (d, 1H, J = 12.1 Hz), 3.42 (dd, 1H, J_1 = 10.3, J_2 = 6.2 Hz), 3.31 (dd, 1H, J_1 = 10.3, J_2 = 7.0 Hz), 1.40 (s, 3H), 1.38 (s, 3H), 1.32—1.22 (m, 1H), 0.81—0.74 (m, 2H), 0.54 (ddd, 1H, J_1 = 11.4, J_2 = 5.5, J_3 = 4.4 Hz); ^{13}C NMR δ = 138.3, 128.3, 127.51, 127.45, 123.1, 72.6, 72.5, 43.1, 26.6, 26.5, 25.6, 15.8, 7.6; IR (neat) 2850, 2225, 1450, 1360, 1240, 1200, 1100, 1022, 740, 700 cm^{-1}. HRMS Found: *m/z* 229.1487. Calcd for $C_{15}H_{19}NO$: M^+, 229.1467.

Cyclopropane 26: The cyclization protocol described for the synthesis of **10** was applied for **9** (93.1 mg, 0.423 mmol) by using *s*-collidine (76.9 mg, 0.634 mmol) and triflic anhydride (179 mg, 0.634 mmol) in CH_2Cl_2 (8.0 ml) at −78 °C. After 15 min, triisobutylaluminum (1.04 M in hexane, 1.40 ml, 1.46 mmol) was added, and the reaction was warmed to −30 °C in 1 h. Purification with silica-gel preparative TLC (hexane/EtOAc = 19/1) gave **26** (70.7 mg, 82%) as colorless oil; ^{1}H NMR δ = 7.35—7.25 (m, 5H), 4.53 (s, 2H), 3.40 (dd, 1H, J_1 = 10.3, J_2 = 6.6 Hz), 3.23 (dd, 1H, J_1 = 10.3, J_2 = 7.3 Hz), 1.00—0.84 (m, 8H), 0.43—0.32 (m, 3H); ^{13}C NMR δ = 138.7, 128.3, 127.6, 127.4, 74.4, 72.3, 32.5, 25.4, 22.2, 21.9, 17.4, 9.5; IR (neat) 2975, 2875, 1500, 1450, 1360, 1200, 1170, 1100, 1070, 1020, 740, 700 cm^{-1}. HRMS Found: *m/z* 204.1545. Calcd for $C_{14}H_{20}O$: M^+, 204.1512.

Typical Procedure for the Syntheses of Vinylcyclopropanes Is Described for the Synthesis of Vinylcyclopropane 11. To a mixture of homoallyl alcohol **9** (90.5 mg, 0.411 mmol) and *s*-collidine (68.8 mg, 0.568 mmol) in CH_2Cl_2 (7.0 mL) at −78 °C was slowly added triflic anhydride (157 mg, 0.557 mmol) in CH_2Cl_2 (1.0 ml). After 15 min, Et_3N (125 mg, 1.23 mmol) was added and the reaction was gradually warmed to room temperature. After adding sat. $NaHCO_3$ aq solution, the products were extracted with EtOAc, and the combined extracts were washed with brine and dried (Na_2SO_4). Purification with silica-gel preparative TLC (hexane/EtOAc=9/1) gave **11** (74.8 mg, 90%) as colorless oil; ^{1}H NMR δ = 7.35—7.25 (m, 5H), 4.71—4.70 (m, 1H), 4.69—4.67 (m, 1H), 4.56 (d, 1H, J = 12.1 Hz), 4.52 (d, 1H, J = 12.1 Hz), 3.42 (dd, 1H, J_1 = 10.2, J_2 = 6.6 Hz), 3.33 (dd, 1H, J_1 = 10.2, J_2 = 6.6 Hz), 1.65—1.64 (m, 3H), 1.31 (ddd, 1H, J_1 = 8.4, J_2 = J_3 = 5.1 Hz), 1.27—1.20 (m, 1H), 0.78 (ddd, 1H, J_1 = 8.4, J_2 = J_3 = 5.1 Hz), 0.58 (ddd, 1H, J_1 = 8.4, J_2 = J_3 = 5.1 Hz); ^{13}C NMR δ = 145.3, 138.5, 128.4, 127.6, 127.5, 108.6, 73.7, 72.4, 23.6, 20.5, 18.8, 10.5; IR (neat) 2890, 1640, 1500, 1450, 1360, 1250, 1200, 1170, 1100, 1030, 870, 720, 700 cm^{-1}. HRMS Found: *m/z* 202.1384. Calcd for $C_{14}H_{18}O$: M^+, 202.1358.

Vinylcyclopropane 14: The cyclization protocol described for the synthesis of **11** was applied for **13** (82.4 mg, 0.352 mmol) by using *s*-collidine (80.5 mg, 0.665 mmol) and triflic anhydride (187 mg, 0.663 mmol) in CH_2Cl_2 (5.0 ml) at −78 °C. After 20 min, triethylamine (117 mg, 1.16 mmol) was added, and the reaction was warmed to room temperature. Purification with silica-gel preparative TLC (hexane/EtOAc=4/1) gave **14** (64.8 mg, 85%) as colorless oil; ^{1}H NMR δ = 7.34—7.24 (m, 5H), 4.68 (d, 1H, J = 1.7 Hz), 4.67 (d, 1H, J = 1.7 Hz), 4.64 (d, 1H, J = 11.9 Hz), 4.54 (d, 1H, J = 11.9 Hz), 3.00 (dq, 1H, J_1 = 7.9, J_2 = 6.3 Hz), 1.65 (s, 3H), 1.30 (d, 3H, J = 6.3 Hz), 1.17 (ddd, 1H, J_1 = 8.9, J_2 = J_3 = 5.0 Hz), 1.06—0.96 (m, 1H), 0.86 (ddd, 1H, J_1 = 8.6, J_2 = 5.3, J_3 = 5.0 Hz), 0.71 (ddd, 1H, J_1 = 8.9, J_2 = 5.3, J_3 = 5.0 Hz), ^{13}C NMR δ = 145.4, 139.0, 128.3, 127.5, 127.3, 108.4, 78.2, 70.2, 24.8, 21.7, 20.6, 20.3, 12.0; IR (neat) 2990, 1640, 1500, 1455, 1375, 1200, 1100, 880, 740, 700 cm^{-1}. HRMS Found: *m/z* 216.1523. Calcd for $C_{15}H_{20}O$: M^+, 216.1514.

Vinylcyclopropane 17: The cyclization protocol described for the synthesis of **11** was applied for **16** (123 mg, 0.526 mmol) by using *s*-collidine (128 mg, 1.05 mmol) and triflic anhydride (289 mg, 1.02 mmol) in CH_2Cl_2 (5.0 ml) at −78 °C. After 25 min, triethylamine (159 mg, 1.57 mmol) was added, and the reac-

tion was warmed to room temperature. Purification with silica-gel preparative TLC (hexane/EtOAc=4/1) gave **17** (94.7 mg, 83%) as colorless oil; ^{1}H NMR δ = 7.36—7.24 (m, 5H), 4.74 (m, 1H), 4.67 (m, 1H), 4.67 (d, 1H, J = 12.1 Hz), 4.53 (d, 1H, J = 12.2 Hz), 2.98 (dq, 1H, J_1 = 8.1, J_2 = 6.2 Hz), 1.66 (s, 3H), 1.42 (ddd, 1H, J_1 = 9.1, J_2 = J_3 = 5.1 Hz), 1.28 (d, 3H, J = 6.3 Hz), 1.06—1.00 (m, 1H), 0.71 (ddd, 1H, J_1 = 9.1, J_2 = J_3 = 5.1 Hz), 0.43 (ddd, 1H, J_1 = 8.1, J_2 = J_3 = 5.1 Hz); ^{13}C NMR δ = 145.3, 139.1, 128.3, 127.5, 127.3, 108.6, 78.0, 70.0, 25.3, 24.5, 20.3 (2C), 8.4; IR (neat) 2975, 1710, 1630, 1495, 1440, 1370, 1200, 1100, 870, 730, 695 cm^{-1}. HRMS Found: m/z 216.1517. Calcd for $C_{15}H_{20}O$: M$^+$, 216.1514.

Trisubstituted Vinylcyclopropane 28: The cyclization protocol described for the synthesis of **11** was applied for homoallyl alcohol **27** (99.1 mg, 0.454 mmol) by using s-collidine (121 mg, 1.00 mmol) and triflic anhydride (264 mg, 0.936 mmol) in CH_2Cl_2 (9.0 ml) at −78 °C. After 30 min, triethylamine (147 mg, 1.46 mmol) was added, and the reaction was warmed to room temperature. Purification with silica-gel preparative TLC (hexane) gave **28** (56.3 mg, 62%) as colorless oil; $[\alpha]_D^{22}$ +6.3 (c 1.10, $CHCl_3$); ^{1}H NMR δ = 7.29—7.15 (m, 5H), 4.59 (s, 2H), 2.76—2.04 (m, 2H), 1.77—1.62 (m, 2H), 1.61 (s, 3H), 1.06 (d, 3H, J = 5.8 Hz), 0.98 (ddq, 1H, J_1 = 8.8, J_2 = 5.1, J_3 = 5.8 Hz), 0.90 (ddt, 1H, J_1 = 8.8, J_2 = 5.1, J_3 = 7.0 Hz), 0.78 (dd, 1H, J_1 = J_2 = 5.1 Hz) (These data were obtained by the aid of J-resolved 2D experiment.); ^{13}C NMR δ = 146.9, 142.5, 128.5, 128.3, 125.7, 106.8, 36.3, 33.3, 30.3, 24.1, 21.1, 18.0, 12.8; IR (neat) 2830, 1635, 1500, 1450, 1370, 1240, 1070, 870, 750, 700 cm^{-1}. HRMS Found: m/z 200.1573. Calcd for $C_{15}H_{20}$: M$^+$, 200.1565. The enantiomeric excess of **28** (>99%) was determined by its chiral GC analysis, which was carried out by using 50 m×0.25 mm CP-Cyclodextrin-β-2,3,6-M-19 capillary column (CHROMPACK).

Typical Procedure for the Ozonolysis Is Described for the Synthesis of Cyclopropyl Methyl Ketone 12. Ozone (0.594 mmol) was passed through a solution of vinylcyclopropane **11** (118 mg, 0.584 mmol) in methanol (5.0 ml) at −78 °C for 9.5 min followed by dimethyl sulfide (0.4 ml) was added. The reaction was gradually warmed to room temperature. Removal of the solvents gave a crude product, which was purified with silica-gel preparative TLC chromatography (hexane/EtOAc = 4/1) to gave cyclopropyl methyl ketone **12** (118 mg, 99%) as colorless oil; ^{1}H NMR δ = 7.38—7.24 (m, 5H), 4.53 (d, 1H, J = 12.2 Hz), 4.48 (d, 1H, J = 12.2 Hz), 3.48 (dd, 1H, J_1 = 10.6, J_2 = 5.9 Hz), 3.31 (dd, 1H, J_1 = 10.6, J_2 = 6.9 Hz), 2.23 (s, 3H), 1.89 (ddd, 1H, J_1 = 8.3, J_2 = J_3 = 4.3 Hz), 1.81—1.69 (m, 1H), 1.25 (ddd, 1H, J_1 = 8.4, J_2 = 4.3, J_3 = 4.0 Hz), 0.89 (ddd, 1H, J_1 = 8.3, J_2 = 6.3, J_3 = 4.0 Hz); ^{13}C NMR δ = 207.5, 188.1, 128.4, 127.7, 127.6, 72.6, 71.6, 30.4, 26.9, 24.1, 15.2; IR (neat) 2870, 1700, 1450, 1360, 1315, 1250, 1170, 1080, 740, 700 cm^{-1}. HRMS Found: m/z 204.1117. Calcd for $C_{13}H_{16}O_2$: M$^+$, 204.1150.

Cyclopropyl Methyl Ketone 15: Vinylcyclopropane **14** (36.4 mg, 0.169 mmol) was subjected to the ozonolysis as above to give **15** (30.0 mg, 82%) as colorless oil; ^{1}H NMR δ = 7.38—7.24 (m, 5H), 4.58 (d, 1H, J = 11.9 Hz), 4.53 (d, 1H, J = 11.9 Hz), 3.22 (dq, 1H, J_1 = 6.6, J_2 = 6.3 Hz), 2.22 (s, 3H), 1.82 (ddd, 1H, J_1 = 8.2, J_2 = 4.6, J_3 = 4.0 Hz), 1.72—1.54 (m, 1H), 1.30 (ddd, 1H, J_1 = 8.6, J_2 = 4.6, J_3 = 4.0 Hz), 1.26 (d, 3H, J = 6.3 Hz), 1.02 (ddd, 1H, J_1 = 8.2, J_2 = 6.6, J_3 = 4.0 Hz); ^{13}C NMR δ = 207.7, 138.6, 128.3, 127.5 (2C), 75.4, 70.3, 30.2, 29.7, 25.2, 19.8, 15.9; IR (neat) 2975, 1700, 1500, 1450, 1360, 1170, 1100, 965, 740, 700 cm^{-1}. HRMS Found: m/z 218.1328. Calcd for $C_{14}H_{18}O_2$: M$^+$, 218.1307.

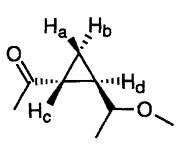
Cyclopropyl Methyl Ketone 18: Vinylcyclopropane **17** (180 mg, 0.833 mmol) was subjected to the ozonolysis as above to give **18** (142 mg, 78%) as colorless oil; ^{1}H NMR δ = 7.38—7.26 (m, 5H), 4.57 (d, 1H, J = 12.2 Hz), 4.50 (d, 1H, J = 12.2 Hz), 3.18 (dq, 1H, J_1 = J_2 = 6.3 Hz), 2.23 (s, 3H), 1.96 (ddd, 1H, J_1 = 8.3, J_2 = J_3 = 4.3 Hz), 1.63—1.53 (m, 1H), 1.28 (d, 3H, J = 6.3 Hz), 1.22 (ddd, 1H, J_1 = 8.6, J_2 = 4.3, J_3 = 4.0 Hz), 0.85 (ddd, 1H, J_1 = 8.3, J_2 = 6.6, J_3 = 4.0 Hz); ^{13}C NMR δ = 207.6, 138.7, 128.4, 127.6, 127.5, 75.4, 70.3, 30.33, 30.28, 27.3, 19.9, 13.7; IR (neat) 2975, 1700, 1500, 1450, 1360, 1170, 1100, 965, 740, 700 cm^{-1}. HRMS Found: 218.1308. Calcd for $C_{14}H_{18}O_2$: M$^+$, 218.1307.

Trisubstituted Cyclopropyl Methyl Ketone 29: Vinylcyclopropane **28** (83.0 mg, 0.415 mmol) was subjected to the ozonolysis as above to give **29** (72.0 mg, 86%) as colorless oil; $[\alpha]_D^{20}$ +46.9 (c 1.03, $CHCl_3$); ^{1}H NMR δ = 7.29—7.14 (m, 5H), 2.79—2.60 (m, 2H), 2.08 (s, 3H), 1.84—1.44 (m, 4H), 1.30 (dd, 1H, J_1 = J_2 = 4.3 Hz), 1.05 (d, 3H, J = 5.9 Hz); ^{13}C NMR δ = 208.1, 141.7, 128.5, 128.4, 125.9, 37.4, 35.8, 30.7, 30.4, 29.3, 24.5, 12.2; IR (neat) 2950, 1695, 1600, 1500, 1420, 1360, 1325, 1180, 1065, 1030, 995, 750, 700 cm^{-1}. HRMS Found: m/z 202.1372. Calcd for $C_{14}H_{18}O$: M$^+$, 202.1357.

Epoxy Lactone 31: To a solution of hydroxy ester **30** (170 mg, 0.977 mmol) in benzene (50 ml) was added a catalytic amount of p-toluenesulfonic acid monohydrate, and the mixture was refluxed for 20 min. After cooling to room temperature, sat. $NaHCO_3$ aq solution was added, and the product was extracted with EtOAc (×3). The combined extracts were washed with brine and dried (Na_2SO_4). Purification with silica-gel column chromatography (hexane/acetone = 7/3) gave epoxy lactone **31** (112 mg, 81%) as colorless oil; $[\alpha]_D^{24}$ +43.5 (c 1.04, $CHCl_3$); ^{1}H NMR δ = 4.13 (ddd, 1H, J_1 = 10.3, J_2 = 5.5, J_3 = 3.7 Hz), 3.11 (ddd, J_1 = 5.5, J_2 = 4.0, J_3 = 2.6 Hz), 2.88 (dd, 1H, J_1 = 4.8, J_2 = 4.0 Hz), 2.74 (dd, 1H, J_1 = 4.8, J_2 = 2.6 Hz), 2.66—2.58 (m, 1H), 2.51 (ddd, 1H, J_1 = 17.9, J_2 = 9.2, J_3 = 6.6 Hz), 2.07—1.96 (m, 2H), 1.93—1.82 (m, 1H), 1.80—1.70 (m, 1H); ^{13}C NMR δ = 170.3, 80.2, 52.4, 45.6, 29.6, 24.4, 18.0; IR (neat) 3050, 2950, 1728, 1640, 1440, 1348, 1239, 1170, 1050, 930, 850, 760 cm^{-1}. HRMS Found: 142.0615. Calcd for $C_7H_{10}O_3$: M$^+$. 142.0630.

Homoallyl Alcohol 32: 2-Methyl-1-propenyllithium, which was prepared from butyllithium (1.40 ml, 1.60 M in hexane) and 2-methyl-1-propenyltributylstannane (804 mg, 2.33 mmol) in THF (3.0 ml at 0 °C), was added to suspension of copper cyanide (101 mg, 1.12 mmol) in ether (8.0 ml) at −78 °C. After 4 min, the reaction was warmed to 0 °C and stirred for 3 min. The cuprate prepared was rechilled to −78 °C, and a solution of epoxy lactone **31** (80.3 mg, 0.565 mmol) in ether (2.0 ml) was added. After the reaction was gradually warmed up to −20 °C and stirred for 1 min, the mixture was poured into sat. NH_4Cl aq solution, and the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine and dried (Na_2SO_4). Purification with silica-gel column chromatography (hexane/acetone = 4/1) gave homoallyl alcohol **32** (70.1 mg, 63%) as colorless oil; $[\alpha]_D^{25}$ +29.3 (c 0.805, $CHCl_3$); ^{1}H NMR δ = 5.18—5.13 (m, 1H), 4.62 (dt, 1H, J_1 = 10.6, J_2 = 4.0 Hz), 3.81 (ddd, 1H, J_1 = 10.6, J_2 = 6.6, J_3 = 4.0 Hz), 2.64—2.57 (m, 1H), 2.50—2.41 (m, 2H), 2.26 (t, 2H, J = 7.0 Hz), 2.02—1.92 (m, 2H), 1.89—1.76 (m, 2H), 1.74 (S, 3H), 1.65 (S, 3H); ^{13}C NMR δ = 171.7, 135.5, 118.9, 82.7, 72.3, 30.9, 29.7, 25.8, 21.6, 18.2, 17.9; IR (neat) 3425, 2920, 1720, 1440, 1360, 1245, 1170, 1050, 935 cm^{-1}. HRMS Found: m/z 198.1266. Calcd for $C_{11}H_{18}O_3$: M$^+$, 198.1256.

Cyclopropyl Methyl Ketone 34: To a mixture of homoallyl alcohol **32** (52.7 mg, 0.266 mmol) and s-collidine (67.9 mg, 0.561 mmol) in CH_2Cl_2 (4.0 ml) at −78 °C was slowly added triflic anhydride (162 mg, 0.576 mmol) in CH_2Cl_2 (1.0 ml). After 1 h,



$J_{a,b} = 4.4$ Hz
$J_{a,c} = 8.4$ Hz
$J_{a,d} = 6.2$ Hz
$J_{b,c} = 4.4$ Hz
$J_{b,d} = 9.2$ Hz
$J_{c,d} = 4.4$ Hz

Fig. 4. Coupling constants between the hydrogens on the cyclopropane ring in **34**.

Et_3N (103 mg, 1.01 mmol) was added and the reaction was gradually warmed to room temperature. After the reaction was stopped by the addition of sat. $NaHCO_3$ aq solution, the products were extracted with EtOAc, and the combined organic extracts were successively washed with sat. $CuSO_4$ aq solution, sat. $NaHCO_3$ aq solution, and brine and dried (Na_2SO_4). Solvents were removed under reduced pressure, and the residue was dissolved in methanol (6.0 ml). Ozone (0.438 mmol) was passed through the solution at −78 °C for 7 min, and dimethyl sulfide (0.4 ml) was added to the mixture. The reaction was gradually warmed to room temperature. After stirring for 1 h, removal of the solvents afforded the crude product, which was purified with silica-gel column chromatography (hexane/acetone = 7/3) to give cyclopropyl methyl ketone **34** (43.5 mg, 90%) as pale yellow oil; $[\alpha]_D^{24}$ −97.2 (*c* 1.07, $CHCl_3$); ^{1}H NMR δ = 3.80 (ddd, 1H, J_1 = 10.3, J_2 = 7.7, J_3 = 3.3 Hz), 2.63—2.55 (m, 1H), 2.48 (ddd, 1H, J_1 = 17.9, J_2 = 8.8, J_3 = 7.0 Hz), 2.31 (s, 3H), 2.12 (ddd, 1H, J_1 = 8.4, $J_2 = J_3$ = 4.4 Hz), 2.08—1.93 (m, 2H), 1.89—1.78 (m, 1H), 1.75—1.66 (m, 2H), 1.28 (ddd, 1H, J_1 = 9.2, $J_2 = J_3$ = 4.4 Hz), 0.95 (ddd, 1H, J_1 = 8.4, J_2 = 6.2, J_3 = 4.4 Hz); ^{13}C NMR δ = 207.0, 171.1, 81.9, 30.8, 29.4, 28.3, 27.9, 26.0, 18.3, 14.0; IR (neat) 3000, 2940, 1727, 1693, 1415, 1380, 1350, 1235, 1175, 1040, 965, 930, 860, 755 cm^{-1}. HRMS Found: *m/z* 182.0933. Calcd for $C_{10}H_{14}O_3$: M^+, 182.0943. The *trans*-stereochemistry was determined by the coupling constants between the hydrogens on the cyclopropane ring of **34** (Fig. 4).

Aldol 35: A solution of cyclopropyl methyl ketone **34** (29.3 mg, 0.161 mmol) in CH_2Cl_2 (2.0 ml) was added to a mixture of dibutylboron triflate (1.0 M in CH_2Cl_2, 0.24 mL, 0.24 mmol) and diisopropylethylamine (31.8 mg, 0.246 mmol) in CH_2Cl_2 (4.0 ml) at −78 °C. After 30 min, a solution of (*Z*)-4-decenal (30.3 mg, 0.197 mmol) in CH_2Cl_2 (1.0 ml) was added and stirred for 1 h. The reaction was quenched by adding pH 7 phosphate buffer. The products were extracted with ether (×3). After removal of the solvents, the residue was dissolved in methanol (3.0 ml), to which was added 35% H_2O_2 (1.0 ml). After stirring for 1 h, water was added to the mixture, and the products were extracted with EtOAc (×3). The combined organic extracts were washed with sat. $NaHCO_3$ aq solution and brine, and dried (Na_2SO_4). Purification with silica-gel chromatography (hexane/EtOAc = 7/3) to give aldol **35** (31.0 mg, 57%) as colorless oil, and aldol **36** (11.2 mg, 14%) was also obtained. **35**: ^{1}H NMR δ = 5.43—5.32 (m, 2H), 4.12—4.01 (m, 1H), 3.85 (ddd, J_1 = 10.6, J_2 = 7.3, J_3 = 3.3 Hz) and 3.77 (ddd, J_1 = 10.3, J_2 = 8.1, J_3 = 3.3 Hz) (1H), 3.03 (b, 1H), 2.90—2.67 (m, 2H), 2.62—2.43 (m, 2H), 2.22—2.09 (m, 2H), 2.07—1.92 (m, 4H), 1.89—1.78 (m, 1H), 1.77—1.67 (m, 2H), 1.65—1.53 (m, 2H), 1.49—1.40 (m, 1H), 1.36—1.25 (m, 7H), 1.02 (ddd, J_1 = 8.1, J_2 = 6.2, J_3 = 4.0 Hz) and 0.97 (ddd, J_1 = 8.1, J_2 = 6.2, J_3 = 4.0 Hz) (1H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ = 210.1, 209.9, 171.1, 171.0, 130.8, 128.7, 82.1, 81.4, 67.2, 67.1, 50.3, 50.2, 36.3, 36.2, 31.5, 29.5, 29.3, 28.7, 28.0, 27.9, 27.1, 26.1, 25.9, 23.2, 22.5, 18.4, 14.3, 14.0; IR (neat) 3450, 3000, 2910, 2850, 1720, 1690, 1440, 1380, 1238, 1037, 928 cm^{-1}. HRMS Found: *m/z* 337.2367. Calcd for $C_{20}H_{33}O_4$: $(M+H)^+$, 337.2379.

Lactone 37: To a solution of aldol **35** (18.5 mg, 0.0551 mmol) in CH_2Cl_2 (2.0 ml) was added triethylamine (28.0 mg, 0.277 mmol) followed by methanesulfonyl chloride (23.3 mg, 0.203 mmol) at 0 °C. After stirring for 30 min, DBN (35.4 mg, 0.285 mmol) was added to the mixture. After warming to room temperature, the mixture was stirred for 1 h. Phosphate buffer (pH 7) was added and, the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine and dried (Na_2SO_4). The products were purified with silica-gel preparative TLC (hexane/EtOAc = 2/3) to give lactone **37** (16.0 mg, 91%) as colorless oil; $[\alpha]_D^{21}$ −30.0 (*c* 0.840, $CHCl_3$); ^{1}H NMR δ = 6.94 (dt, 1H, J_1 = 15.7, J_2 = 6.6 Hz), 6.26 (dt, 1H, J_1 = 15.7, J_2 = 1.5 Hz), 5.43 (dt, 1H, J_1 = 11.0, J_2 = 7.3 Hz), 5.35 (dt, 1H, J_1 = 11.0, J_2 = 6.6 Hz), 3.87 (ddd, 1H, J_1 = 10.6, J_2 = 7.3, J_3 = 3.3 Hz), 2.63—2.55 (m, 1H), 2.47 (ddd, 1H, J_1 = 17.6, J_2 = 8.4, J_3 = 7.0 Hz), 2.33—2.27 (m, 3H), 2.26—2.20 (m, 2H), 2.08—2.00 (m, 3H), 1.98—1.92 (m, 1H), 1.88—1.81 (m, 1H), 1.80—1.66 (m, 2H), 1.38—1.26 (m, 7H), 0.98 (ddd, 1H, J_1 = 8.4, J_2 = 6.2, J_3 = 4.0 Hz), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ = 198.3, 171.1, 147.2, 131.4, 130.6, 127.7, 81.8, 32.6, 31.5, 29.5, 29.3, 28.3, 28.0, 27.2, 25.8, 23.6, 22.5, 18.4, 14.1, 14.0; IR (neat) 3010, 2960, 2925, 2860, 1730, 1680, 1660, 1625, 1445, 1380, 1340, 1240, 1200, 1180, 1040, 980, 930 cm^{-1}. HRMS Found: *m/z* 318.2199. Calcd for $C_{20}H_{30}O_3$: M^+, 318.2195.

Eicosanoid 3: An aqueous solution (1.0 ml) of lithium hydroxide monohydrate (7.1 mg, 0.17 mmol) was added to a solution of lactone **37** (10.7 mg, 33.6 μmol) in THF (3.0 ml) at 0 °C. After 10 min, water (2.0 ml) and 0.5 M H_2SO_4 (0.2 ml) was added, and the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine and dried (Na_2SO_4). Purification with silica-gel preparative TLC (hexane/acetone = 1/1) to give eicosanoid **3** (11.3 mg, quant.) as colorless oil; ^{1}H NMR δ = 6.93 (dt, 1H, J_1 = 15.7, J_2 = 6.6 Hz), 6.24 (dt, 1H, J_1 = 15.7, J_2 = 1.5 Hz), 5.46—5.30 (m, 2H), 3.22 (dt, 1H, J_1 = 5.1, J_2 = 7.3 Hz), 2.41 (t, 2H, J = 7.3 Hz), 2.30—2.17 (m, 5H), 2.02 (dt, 2H, $J_1 = J_2$ = 7.0 Hz), 1.86—1.60 (m, 5H), 1.38—1.26 (m, 8H), 0.93 (ddd, 1H, J_1 = 8.4, J_2 = 6.6, J_3 = 4.0 Hz), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ = 199.2, 178.3, 146.9, 131.4, 130.5, 127.7, 73.4, 36.4, 33.6, 32.6, 31.5, 31.2, 29.2, 27.2, 25.8, 23.7, 22.5, 20.7. 15.2, 14.0; IR (neat) 3400 (br), 3025, 2940, 2860, 1715, 1630, 1625, 1450, 1410, 1250, 1210, 1120, 1080, 980, 935 cm^{-1}.

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13) Preliminary experiments were carried out also for the corresponding mesylates. The major difference was that the mesylates can be isolated without undergoing the cyclization. It is interesting to compare the behaviors of homoallyl mesylates **38**, **41**, and **43** with varying degree of γ-substitution in the reaction with Me_3Al (in toluene, −78→0 °C; Table 2). Non-substituted one **38** gave the product **39** by the homoallylic participation and the methylation. However, an additional product **39** arose from the further skeletal change before undergoing the methylation.[10a] Mono-methylated one **41** underwent the cyclization–methylation to give the isopropyl substituted product **42** in high yield. Bis-methylated one **43** underwent methylation to give *t*-butyl substituted cyclopropane **44** in high yield as a sole diastereomer.

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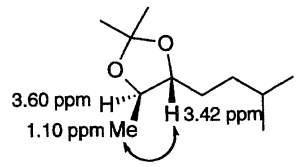

Fig. 5. NOE of the cyclic acetal derived from **13**.

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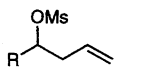
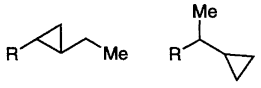
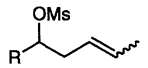
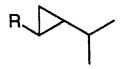
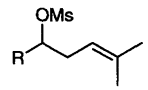
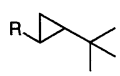
Table 2.

Mesylate	Product(s)
 **38** R = CH_2CH_2Ph	 **39** **40** **39/40** = 2/3 (84% combined yield)
 **41**	 **42** 96% (*trans*/*cis* = 96 / 4)
 **43**	 **44** 85%