On the Enantioselectivity of a 2-Aza-divinylcyclopropane Rearrangement

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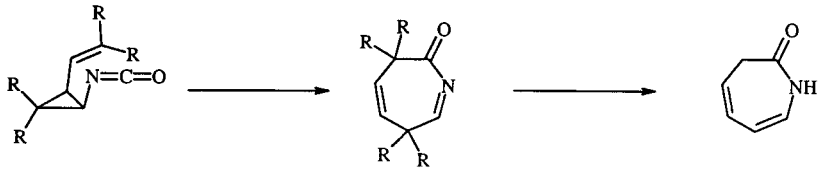
The optically active cyclopropanecarbonyl azide **6** (ee 90%) was synthesized from the known cyclopropanecarboxylate **4**. Upon heating in refluxing benzene, **6** rearranged to the dihydroazepinone **9** (ee 65%) *via* the isocyanate **7** and the enamide **8**. In contrast, the dimethyl-substituted cyclopropanecarbonyl azide **20** rearranged to the isocyanate **21**, but decomposed at higher temperatures rather than to undergo *Cope* rearrangement to **22**. The results are consistent with a mechanism involving a boat-like *endo*-transition state **11** for the rearrangement, which may not be reached with the dimethyl derivative **21** for steric reasons. The origin of change in enantiomer composition, upon going from **6** to **9**, is at present unknown.

Introduction. – The rearrangement of *cis*-divinylcyclopropanes to cyclohepta-1,3-dienes is a variant of the *Cope* rearrangement [1]. The driving force of the reaction is provided by the release of ring strain of the cyclopropane ring in the course of the transformation. The rearrangement is concerted and stereospecific, and it occurs at relatively low temperatures ($< 35°$ in the case of the parent *cis*-1,2-divinylcyclopropane [2]) through a boat-like *endo*-transition state [3]. The *exo*-transition state is disfavored, because it would afford a highly strained (*E*,*E*)-cyclohepta-1,3-diene. If, for steric reasons, the *endo*-transition state may not be reached, the reaction does not take place, and *cis/trans*-isomerization of the cyclopropane can occur instead [4]. *trans*-Divinylcyclopropanes may still rearrange to cycloheptadienes, but these reactions require much higher temperatures (170° for *trans*-divinylcyclopropane [5]) and proceed probably through a biradical mechanism [6]. The divinylcyclopropane rearrangement has found numerous applications in organic synthesis, and the reaction has been reviewed in 1989 and 1992 [7]. Recent asymmetric versions involving cyclopropanation of dienes by vinyldiazoacetates and subsequent *Cope* rearrangement of the adducts allow highly enantioselective syntheses of cycloheptadienes containing multiple stereogenic centers [8].

In 1958, *Doering* and *Goldstein* reported the first aza analogue of the divinylcyclopropane rearrangement [9]. Subsequently, *Vogel* and *Roth* described the rearrangement of the parent *cis*-2-vinylcyclopropyl isocyanate (**1a**) at 80° to 1-azacyclohepta-4,6-diene-2-one (= 2,3-dihydro-1*H*-azepin-2-one; **3**), presumably *via* 1-azacyclohepta-4,7-diene-2-one (= 3,6-dihydro-2*H*-azepin-2-one; **2a**), which underwent tautomerization to **3** [10] (*Scheme 1*). In contrast, *trans*-vinylcyclopropyl isocyanate was stable up to 200°. The reaction mechanism of **1a** was not further investigated; however, the analogy with the divinylcyclopropane rearrangement suggested a concerted process. *Sasaki et al.* found an entropy of activation of $\Delta S^{\neq} = -29$ e.u. for the rearrangement of *cis*-2,2-

dimethyl-3-(2-methylprop-1-enyl)cyclopropyl isocyanate (**1b**) to the azepinone **2b**. This value is consistent with a highly ordered transition state, and lies within the expected range for rearrangements of *cis*-divinylcyclopropanes [11]. Although the available evidence suggests that the divinylcyclopropane rearrangement and its aza analogue proceed *via* the same mechanism, this hypothesis has never been verified. In particular, no such rearrangements with optically active isocyanates have been reported to date, which would allow conclusions on the stereochemical course of the reaction.

Scheme 1



1a R = H
1b R = Me

2a R = H
2b R = Me

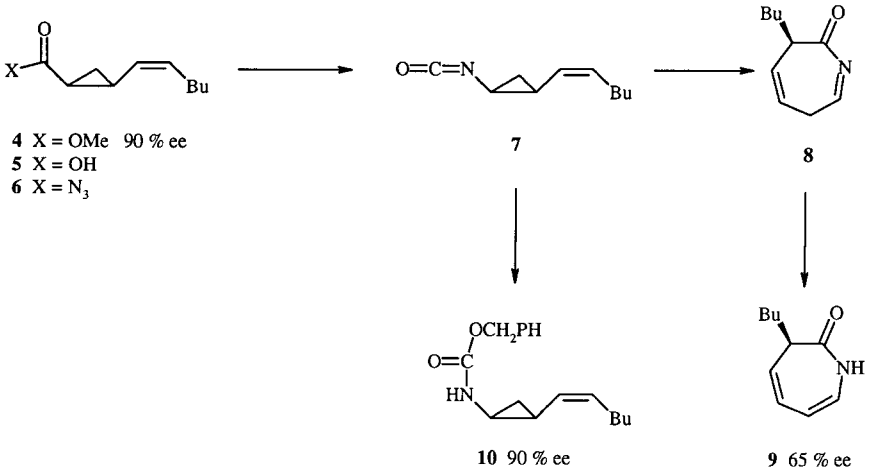
3

We have recently described a simple access to functionalized enantiomerically pure *cis*-cyclopropanecarboxylates *via* cyclopropenation of terminal acetylenes [12] and stereoselective catalytic hydrogenation of the resulting cyclopropenes [13]. This sequence offers a convenient access to optically active *cis*-cyclopropyl isocyanates derived from **1**. We have now applied these compounds to an investigation of the sterochemistry of the '2-aza-divinylcyclopropane' rearrangement.

Results and Discussion. – *Synthesis and Rearrangement of* cis-*2-[(Z)-Hex-1-enyl]-2-cyclopropanecarbonyl azide* (**6**). The synthesis of the desired isocyanate **7** was attempted from methyl *cis*-vinylcyclopropanecarboxylate **4** which, in turn, was obtained with 90% ee as described in [12][13] (*Scheme 2*). Hydrolysis of the ester function of **4** afforded the carboxylic acid **5**. Exposure of **5** to diphenylphosphoryl azide gave the acyl azide **6** with an ee of 90%. When **6** was heated in refluxing benzene (6–12 h) under the conditions required to provoke the *Curtius* rearrangement to the isocyanate **7**, the expected product could not be isolated, since it reacted further to 6-butyl-1-azacyclohepta-2,4-dien-7-one (= 3-butyl-2,3-dihydro-1*H*-azepin-2-one; **9**). Surprisingly, however, the ee of **9** was only 67%, indicating partial (26%) racemization in the course of the process.

The conversion of **6** to **9** may be formulated in analogy to that of **1a**: *Curtius* rearrangement affords the isocyanate **7**, which undergoes an 'aza-divinylcyclopropane' rearrangement to **8**. Tautomerization of **8** finally produces **9**. Partial loss of optical activity may occur at all of the intermediate steps of the sequence under conditions of the reaction, or in the final product **9**. This latter hypothesis was eliminated by refluxing **9** in benzene for 40 h. No change in ee was observed, although some of the material decomposed. The intermediate isocyanate **7** could not be detected in the reaction mixture after partial conversion of the acyl azide **6**. However, when the *Curtius* rearrangement was carried out in the presence of $PhCH_2OH$ (4 equiv.), **7** was partially intercepted and afforded the carbamate **10** together with **9** in a 1:4 ratio. The ee of **10**

Scheme 2



4 X = OMe 90 % ee
5 X = OH
6 X = N_3

7

8

10 90 % ee

9 65 % ee

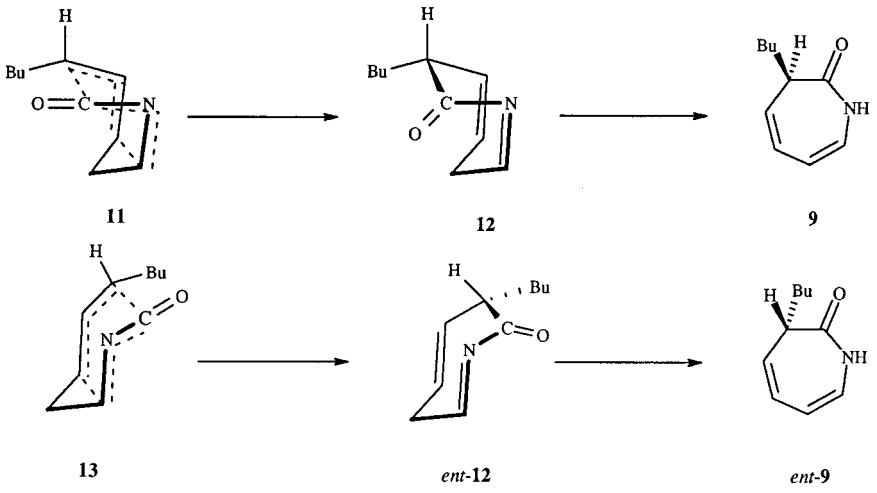
was 90%, and the (*Z*)-configuration of the C=C bond was retained. Similarly, the configuration of the C=C bond in unreacted **6** was not affected under the conditions of the rearrangement. (*Z*/*E*)-isomerization of **6** or **7** would lead to a rearrangement product **9** of opposite configuration. Accordingly, the partial racemization must occur during the rearrangement itself and should have a mechanistic relevance.

A possible cause leading to racemization during the rearrangement of **7** is a biradical pathway competing with the concerted reaction. The occurrence of biradicals in divinylcyclopropane rearrangements is established in the case of *trans*-divinylcyclopropanes, but the biradical pathway is not competititive in the case of rearrangement of the *cis*-isomers [6][7]. The rearrangement of **6** was carried out in the presence of radical traps in the hope that interception of intermediate biradicals would divert them from the rearrangement pathway and, therefore, lead to a higher ee in the product **9**. Galvinoxyl (1.2 equiv.) and diphenyl disulfide (3 equiv.) were used in benzene, and CCl_4 was used as solvent and radical trap at the same time. The yield of **9** was almost unaffected by these modifications, except in the case of galvinoxyl, where it dropped from 59% (without radical trap) to 15%. The ee of **9** showed no significant variations and remained in the range of 65–68%. These negative results are unfortunately not entirely conclusive, since rearrangement of the biradicals may be faster than their reaction with the radical trap. An alternative mechanism for partial racemization, but not involving biradicals, could consist of an (irreversible) homosigmatropic 1,5-H shift of **8** to a 5-azabicyclo[4.1.0]hept-2-en-4-one **13** which, in turn, could undergo non-concerted rearrangement to **9** and *ent*-**9**[1]) (*Scheme 3*). The stereochemical information at C(3) would be lost during this process.

In the carbocyclic version of the divinylcyclopropane rearrangement, the simultaneous presence of two geminal Me groups on the cyclopropane ring and a substituted vinyl group having (*Z*)-configuration blocks the *endo*-transition state efficiently. In

[1]) This possibility was suggested by a reviewer.

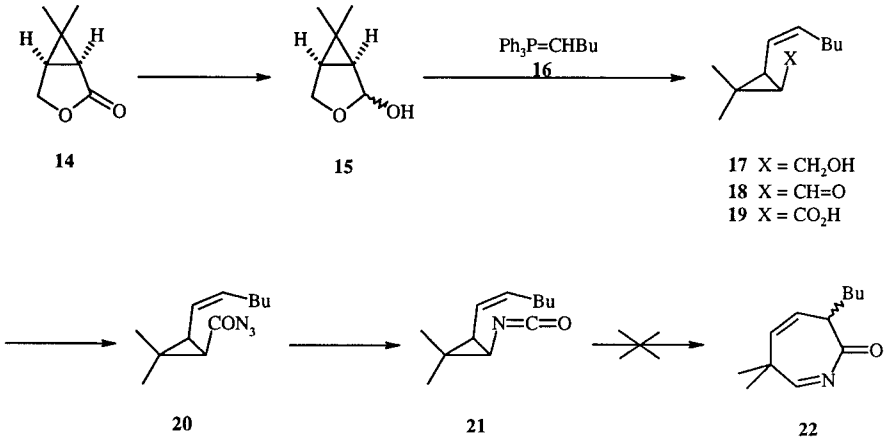
Scheme 3



contrast, in the 2-aza-*Cope* rearrangement **1b** rearranges neatly to **2b** at 144°, but since **2b** is achiral, the question whether it reacts *via* an *endo*-transition state or by a biradical mechanism cannot be investigated. Rearrangement of the optically active (1*S*,2*S*)-**7** affords optically active **9** *via* **8**. If the reaction proceeds through the *endo*-transition state **11**, the absolute configuration of **9** should be (*R*). The absolute configuration of **9** could not be determined due to the insufficient enantiomeric purity of the sample. Therefore, the presumed *endo*-transition state was blocked *via* introduction of Me groups into the cyclopropane ring, with the expectation that this structural modification would result in a mechanistic change.

Synthesis and Attempted Rearrangement of cis-*3-[(Z)-Hex-1-enyl]-2,2-dimethylcyclopropyl Isocyanate* (**21**). The isocyanate **20** was prepared from the known lactone **14** which, in turn, was synthesized with 87% ee *via* asymmetric intramolecular cyclopropanation of dimethylallyl diazoacetate [14]. Reduction of **14** with DIBAH under carefully controlled conditions (– 75°, toluene) afforded the lactol **15** which was added to the phosphorous ylide **16** without isolation [15] (*Scheme 4*). The *cis*/*trans*-selectivity of the *Wittig* reaction was unsatisfactory, and was found strongly dependent upon the base used for deprotonation of the phosphonium-salt precursor. The best results were achieved with *t*-BuOK, which afforded **17** in 47% yield as a 95 : 5 (*Z*)/(*E*)-mixture. With other bases such as BuLi the (*Z*)/(*E*) ratio was 75 : 25. Some lactol **15** was recovered unchanged after workup. A low yield for analogous *Wittig* reactions with lactols has been reported in the literature [16]. The oxidation of the alcohol **17** to the carboxylic acid **19**, which usually is a trivial operation, presented major difficulties. Eventually, it was carried out in two steps, first by conversion of **17** to the aldehyde **18** with pyridinium chlorochromate (PCC), followed by oxidation of **18** with sodium chlorite in phosphate buffer [17]. Since **19** decomposed upon chromatography, it was not further purified, but rather directly converted to the acyl azide **20** by reaction with diphenylphosphoryl azide. The resulting compound **20** was sufficiently stable to allow purification and characterization.

Scheme 4



When **20** was heated in benzene, conversion to the isocyanate **21** could be observed by NMR spectroscopy. However, contrary to the parent azide **6**, which lacks the dimethyl substituents and rearranges directly to **9**, the dimethyl-substituted isocyanate **21** resisted rearrengement further into **22**. Heating **21** to higher temperature (refluxing xylene) resulted in formation of an intractable mixture from which no identifiable product could be isolated. Experiments directed towards trapping of the desired product in the crude reaction mixture with $PhCH_2SH$ or $PhCH_2OH$ were unsuccessful.

The failure of this reaction is surprising in light of the fact that the tetramethyl-substituted vinylcyclopropyl isocyanate **1b** reacts smoothly, although at significantly higher temperature (170°) to the dihydroazepinone **2b** [11], while **20** decomposes before reaching the temperature required for rearrangement. This result, although negative, is mechanistically significant. It indicates strong mechanistic resemblance between the *Cope* rearrangement in the carbocyclic series and its aza variant: The steric hindrance due to the presence of the *geminal* dimethyl group at the cyclopropane ring, together with a (*Z*)-substituted vinyl moiety prevents the molecule to reach the *endo*-transition state **11**, which is a prerequisite for the reaction to occur.

Conclusion. – The 'aza-divinylcyclopropane' rearrangement is to 74% enantioselective, and exhibits striking similarities to the analogous rearrangement in the carbocyclic series. The available evidence suggests an *endo*-transition state **11** for the rearrangement, although this hypothesis requires confirmation by determination of the absolute configuration of the azepinone **9**. Experiments to account for the partial decrease of ee value during the rearrangement were so far not conclusive.

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Experimental Part

General: See [18].

Synthesis of (1S,2S)-2-[(Z)-Hex-1-enyl]cyclopropane-1-carboxylic Acid (**5**). To a soln. of **4** [13] (400 mg, 2.2 mmol) in MeOH (30 ml) was added NaOH (3N, 3.5 ml), and the mixture was stirred overnight. It was concentrated *in vacuo* (40 Torr), then diluted with H_2O (6.0 ml) and extracted with pentane (4 ml). The aq. layer was acidified with cooled 6N HCl to pH 2, and extracted with AcOEt (3 × 15 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated (50 Torr). The crude product was purified by FC (SiO_2; hexane/AcOEt/MeOH 85:15:3): **5** (351 mg, 95%). Transparent oil. $[\alpha]_D^{20} = +268$ ($c = 0.50$, $CHCl_3$), IR (film): 3021*w* (br.), 2940*w*, 1692*s*, 1447*w*, 1289*m*, 1224*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.0, 3 H); 1.21–1.40 (*m*, 6 H); 1.86–1.97 (*m*, 1 H); 2.09–2.21 (*m*, 3 H); 5.33 (*ddt*, *J* = 11.0, 10.6, 1.4, 1 H); 5.49 (*td*, *J* = 11.0, 7.3, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0 (*q*); 20.2 (*d*); 20.8 (*d*); 22.3 (*t*); 25.2 (*t*); 17.3 (*t*); 31.7 (*t*); 125.5 (*d*); 132.8 (*d*); 180.0 (*s*). MS: 168 (25, M^+), 151 (10), 139 (4), 123 (16), 111 (19), 97 (54), 83 (29), 79 (77), 67 (100), 53 (25). HR-MS: 168.1154 ($C_{10}H_{16}O_2^+$; calc. 168.1150).

(1S,2S)-2-[(Z)-Hex-1-enyl]cyclopropane-1-carbonyl Azide (**6**). To **5** (420 mg, 2.50 mmol) in toluene (15 ml) was added, at 0°, Et_3N (1.4 ml, 10 mmol) followed by diphenylphosphoryl azide (1.08 g, 5.0 mmol). The mixture was stirred for 10 min at 0°, then allowed to reach r.t. After 2 h, it was hydrolyzed with H_2O (8.0 ml) and diluted with Et_2O (30 ml). The aq. layer was extracted with Et_2O (3 × 20 ml). After drying ($MgSO_4$), the org. phase was filtered and concentrated (50 Torr). Purification of the crude product by chromatography (SiO_2; hexane/AcOEt 90:10) afforded **6** (390 mg, 81%). Colorless oil. $[\alpha]_D^{20} = +397$ ($c = 1.0$, $CHCl_3$) for 90% ee (by HPLC; *Chiracel OB-H*, with hexane/i-PrOH 99.5:0.5). IR (film): 2910*w*, 2136*s*, 1703*s*, 1376*s*, 1175*m*, 1082*m*, 1033*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.0, 3 H); 1.29–1.46 (*m*, 6 H); 1.92–1.98 (*m*, 1 H); 2.12–2.17 (*m*, 2 H); 2.20–2.29 (*m*, 1 H); 5.31 (*ddt*, *J* = 11.0, 10.6, 1.3, 1 H); 5.55 (*dt*, *J* = 11.0, 7.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0 (*q*); 16.3 (*t*); 22.2 (*d*); 22.3 (*t*); 23.7 (*d*); 27.4 (*t*); 31.7 (*t*); 125.1 (*d*); 135.1 (*d*); 178.2 (*s*). MS: 193 (1, M^+), 165 (5), 151 (4), 137 (3), 122 (19), 109 (23), 108 (42), 95 (27), 94 (19), 80 (50), 82 (20), 81 (45), 80 (49), 79 (43), 67 (100), 55 (64), 54 (31).

*3-Butyl-2,3-dihydro-1*H*-azepin-2-one* (**9**). The azide **6** (116 mg, 0.60 mmol) was refluxed in degassed benzene under N_2 for 6 h. After cooling, the soln. was concentrated in *vacuo*, and the residue was purified by chromatography (SiO_2; hexane/AcOEt 90:10): **9** (70 mg, 60%). Pale-yellow solid. M.p. 56°. $[\alpha]_D^{22} = +79$ ($c = 1.65$, $CHCl_3$) for 67% ee (by HPLC; *Chiracel OD-H*, hexane/i-PrOH 98.75:1.25). IR ($CHCl_3$): 3390*w*, 2932*w*, 1676*s*, 1563*w*, 1256*m*, 1087*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.92 (*t*, *J* = 7.5, 3 H); 1.31–1.45 (*m*, 4 H); 1.70–1.77 (*m*, 1 H); 2.01–2.10 (*m*, 1 H); 2.30 (*td*, *J* = 7.5, 6.2, 1 H); 5.29 (*ddt*, *J* = 9.3, 5.7, 2.3, 1 H); 6.16 (*ddd*, *J* = 9.3, 4.9, 1.7, 1 H); 6.21 (*dd*, *J* = 8.8, 4.9, 1 H); 5.85 (*dd*, *J* = 8.8, 5.1, 1 H); 8.37 (br. *s*). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0 (*q*); 22.6 (*t*); 28.3 (*t*); 29.6 (*t*); 45.7 (*d*); 114.9 (*d*); 125.3 (*d*); 126.1 (*d*); 127.5 (*d*); 169.0 (*s*). MS: 165 (34, M^+), 136 (15), 122 (16), 109 (84), 107 (100), 96 (12), 95 (12), 94 (30), 80 (65), 67 (16), 53 (22). HR-MS: 165.1158 ($C_{10}H_{15}ON^+$; calc. 165.1154).

Benzyl N*-[(1S,2S)-2-[(Z)-Hex-1-enyl]cyclopropyl]carbamate* (**10**). To the azide **6** (96 mg, 0.50 mmol) in toluene (4.0 ml) was added freshly distilled $PhCH_2OH$ (207 µl, 4 equiv.). The soln. was cooled, degassed, and refluxed under N_2 overnight. The mixture was then concentrated, and the crude product was purified by chromatography (SiO_2; hexane/AcOEt 95:5): **10** (30 mg, 22%). Amorphous solid. M.p. 69°. $[\alpha]_D^{22} = +80$ ($c = 0.70$, $CHCl_3$) for 90% ee (by GC; β-dextrin). IR ($CHCl_3$): 3431*w*, 2928*w*, 1712*s*, 1500*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.53–0.54 (*m*, 1 H); 0.91 (*t*, *J* = 7.4, 3 H); 1.19–1.36 (*m*, 4 H); 1.75–1.81 (*m*, 1 H); 2.19–2.24 (*m*, 2 H); 2.81–2.88 (*m*, 1 H); 4.88 (br. *s*, 1 H); 4.98 (*dd*, *J* = 10.8, 8.9, 1 H); 5.14 (br. *s*, 1 H); 5.55 (*td*, *J* = 10.3, 7.4, 1 H); 7.33–7.39 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.9 (*q*); 4.0 (*t*); 21.3 (*t*); 26.5 (*t*); 27.8 (*d*); 31.7 (*t*); 65.8 (*t*); 124.9 (*d*); 127.8 (*d*); 132.4 (*d*); 135.6 (*s*); 156.1 (*s*); 161.4 (*t*). MS: 273 (1, M^+), 186 (13), 182 (62), 172 (41), 138 (43), 133 (19), 121 (36), 108 (20), 92 (54), 91 (100), 79 (21), 69 (31), 67 (18), 65 (32), 55 (26). HR-MS: 273.1711 ($C_{17}H_{23}O_2N^+$; calc. 273.1729).

(1R,3S-3-[(Z)-Hex-1-enyl]-2,2-dimethylcyclopropane-1-methanol (**17**). To the lactone **14** [14] (1.27 g, 10 mmol, ee 87%) in toluene (30 ml) was added dropwise, at −75°, DIBAH (1M in hexane; 12 ml, 1.2 equiv.). After 15 min, the excess of DIBAH was hydrolyzed with MeOH. The soln. was transferred to the ylide **16** prepared from (pentyl)(triphenyl)phosphonium bromide (9.26 g, 20 mmol) and *t*-BuOK (20 mmol) in THF. The mixture was allowed to stand overnight at 25°. It was hydrolyzed with cooled HCl (5%, 80 ml), and diluted with Et_2O (50 ml). The aq. phase was extracted with Et_2O (3 × 100 ml), the org. phase was filtered and concentrated, and the crude product was subjected to CC (SiO_2; hexane/AcOEt 85:15): **17** (855 mg, 43%) was obtained as transparent oil, contaminated with 2–3% of (*E*)-isomer, together with unreacted *(1S,5R)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-ol* (**15**). *Data of* **17**: $[\alpha]_D^{20} = -35$ ($c = 1.0$, $CHCl_3$) for 87% ee. IR (film):

3346*s* (br.), 2963*s*, 2921*s*, 2855*s*, 1451*s*, 1376*m*, 1016*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.4, 3 H); 1.06 (*s*, 3 H); 1.13 (*s*, 3 H); 1.31 – 1.39 (*m*, 5 H); 1.50 (*dd*, *J* = 9.3, 8.4, 1 H); 5.19 (*ddt*, *J* = 10.8, 9.3, 1.5, 1 H); 5.52 (*dtd*, *J* = 10.8, 7.4, 1.5, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.4 (*q*); 15.4 (*q*); 21.3 (*s*); 22.3 (*t*); 25.5 (*q*); 27.4 (*t*); 28.7 (*d*); 31.6 (*d*); 31.7 (*t*); 60.3 (*t*); 124.2 (*d*); 132.8 (*d*). MS: 182 (11, M^+), 152 (20), 151 (88), 139 (26), 109 (44), 107 (25), 96 (23), 95 (100), 93 (37), 81 (67), 79 (40), 77 (26), 71 (27), 69 (67), 67 (71), 55 (83), 53 (29), 57 (30). HR-MS: 182.1676 ($C_{12}H_{22}O^+$; calc. 182.1675).

*(1*R*,3*S*)-3-[(*Z*)-Hex-1-enyl]-2,2-dimethylcyclopropane-1-carbaldehyde* (**18**). To pyridinium chlorochromate (PCC; 2.37 g, 11 mmol), powdered activated molecular sieves (4 Å; 2.0 g), and AcONa (207 mg, 2.5 mmol) in CH_2Cl_2 (20 ml) was added, at 0°, **17** (910 mg, 5.0 mmol) in CH_2Cl_2 within 10 min. The mixture was stirred at 25° for 2 h. It was then diluted with Et_2O (35 ml) and filtered through *Celite*, then through *Florisil*. The residue was washed repeatedly with Et_2O. The filtrate was concentrated, and the crude product was purified by chromatography (SiO_2; hexane/AcOEt 90 : 10): **15** (800 mg, 89%), which was obtained as colorless oil, was contaminated with 5% of the (*E*)-isomer (by NMR). $[\alpha]_D^{20} = -81$ (*c* = 1.1, $CHCl_3$). IR (film): 2942*m*, 2866*w*, 1697*s*, 1378*w*, 1256*w*, 1087*m*, 1016*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89 (*t*, *J* = 6.9, 3 H); 1.21 (*s*, 3 H); 1.25 – 1.36 (*m*, 4 H); 1.37 (*s*, 3 H); 1.80 (*dd*, *J* = 8.4, 6.4, 1 H); 2.08 – 2.13 (*m*, 2 H); 2.15 – 2.19 (*m*, 1 H); 5.58 – 5.62 (*m*, 2 H); 9.41 (*d*, *J* = 6.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.9 (*q*); 15.7 (*q*); 22.3 (*t*); 27.5 (*t*); 28.6 (*q*); 29.8 (*s*); 31.4 (*t*); 34.5 (*d*); 41.2 (*d*); 122.0 (*d*); 134.6 (*d*); 201.5 (*d*). MS: 180 (1, M^+), 151 (80), 123 (19), 109 (26), 95 (100), 81 (33), 77 (13), 69 (35), 67 (40), 57 (15), 55 (41). HR-MS: 180.1533 ($C_{12}H_{20}O^+$; calc. 182.1514).

*(1*R*,3*S*)-3-[(*Z*)-Hex-1-enyl]-2,2-dimethylcyclopropane-1-carboxylic acid* (**19**). To **18** (432 mg, 2.4 mmol) in *t*-BuOH (45 ml) and isobutene (14 ml) was added, in 30 min, $NaClO_2$ (3.25 g, 15 equiv.) and anh. NaH_2PO_4 (2.88 g, 10 equiv.). The mixture was stirred vigorously. After 1.5 h, the solvent and all volatiles were evaporated *in vacuo*. The aq. phase was diluted with H_2O (6 ml) and extracted slowly and repeatedly with AcOEt (10 × 20 ml). The org. layer was dried (Na_2SO_4), filtered, and concentrated. The crude acid was anal. pure; further purification resulted in decomposition. Yield: 376 mg (80%). $[\alpha]_D^{20} = -46°$ (*c* = 1.0, $CHCl_3$). IR (film): 3400 – 2800*s* (br.), 1692*s*, 1447*m*, 1218*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.4, 3 H); 1.22 (*s*, 3 H); 1.26 (*s*, 3 H); 1.32 – 1.37 (*m*, 6 H); 2.04 (*dd*, *J* = 8.4, 8.4, 1 H); 2.12 (*td*, *J* = 6.8, 6.8, 2 H); 5.52 – 5.63 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0 (*q*); 14.7 (*q*); 23.0 (*t*); 27.3 (*t*); 27.6 (*s*); 28.8 (*q*); 31.3 (*d*); 31.7 (*t*); 32.2 (*d*); 122.8 (*d*); 132.8 (*d*); 177.3 (*s*). MS: 196 (21, M^+), 151 (43), 139 (73), 125 (24), 109 (27), 97 (20), 95 (100), 81 (40), 69 (34), 67 (84), 55 (70), 53 (20). HR-MS: 196.1477 ($C_{12}H_{20}O_2^+$; calc. 196.1463).

*(1*R*,3*S*)-3-[(*Z*)-Hex-1-enyl]-2,2-dimethylcyclopropane-1-carbonyl Azide* (**20**). To **19** (160 mg, 0.81 mmol) in toluene (3.0 ml) was added successively, at 0°, Et_3N (460 µl, 3.3 mmol) and diphenylphosphoryl azide (352 µl, 1.6 mmol). The mixture was stirred for 10 min at 0°, then allowed to reach 25°, and then stirred overnight. It was hydrolyzed with H_2O (5.0 ml) and diluted with Et_2O (20 ml). The aq. layer was extracted with Et_2O (3 × 20 ml), the org. layers were dried ($MgSO_4$), filtered, and concentrated (50 Torr). The crude product was purified by chromatography (SiO_2; hexane/AcOEt 96 : 4): **19** (108 mg, 60%). Transparent oil. $[\alpha]_D^{20} = -240$ (*c* = 1.0, $CHCl_3$) for 86% ee (from **14**). IR (film): 2916*w*, 2874*w*, 2134*s*, 1708*s*, 1385*m*, 1118*m*, 1053*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (*s*, 3 H); 0.89 (*t*, *J* = 7.3, 3 H); 1.25 – 1.28 (*m*, 7 H); 1.55 (*d*, *J* = 8.4, 1 H); 2.00 (*dd*, *J* = 9.4, 8.4, 1 H); 2.05 – 2.10 (*m*, 2 H); 5.96 (*ddt*, *J* = 10.9, 9.3, 1.5, 1 H); 5.62 (*dtd*, *J* = 11.0, 7.4, 1.0, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1 (*q*); 22.6 (*q*); 22.6 (*t*); 27.7 (*t*); 28.2 (*q*); 28.3 (*d*); 29.6 (*s*); 32.0 (*t*); 34.5 (*d*); 122.9 (*d*); 133.4 (*d*); 176.5 (*s*). MS: 221 (3, M^+), 193 (20), 151 (42), 150 (53), 136 (55), 122 (75), 108 (60), 95 (100), 94 (53), 93 (62), 91 (39), 79 (57), 77 (37), 67 (67), 55 (72), 53 (42). HR-MS: 221.1526 ($C_{12}H_{19}ON_3^+$; calc. 221.1528).

*(1*R*,3*R*)-3-[(*Z*)-Hex-1-enyl]-2,2-dimethylcyclopropyl Isocyanate* (**21**). The azide **20** (8.0 mg) was heated in C_6D_6 (0.7 ml) to reflux in a NMR tube. Spectra were recorded every 10 min. After 2 h, **20** was converted quantitatively to **21**, which was stable under these conditions. IR (C_6D_6): 2949*m*, 2875*w*, 1228*s*, 2254*s*, 2096*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.79 (*s*, 3 H); 0.91 (*t*, *J* = 7.4, 3 H); 0.94 (*s*, 3 H); 1.28 – 1.38 (*m*, 4 H); 2.04 – 2.11 (*m*, 3 H); 2.30 (*d*, *J* = 7.9, 1 H); 5.20 (*ddt*, *J* = 10.8, 7.4, 1.5, 1 H); 5.65 (*dtd*, *J* = 10.8, 7.4, 1.5, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.8 (*q*); 14.8 (*d*); 21.2 (*s*); 21.7 (*t*); 25.8 (*t*); 26.9 (*q*, *d*); 28.2 (*t*); 31.9 (*t*); 40.7 (*d*); 122.3 (*d*); 135.0 (*d*) (C = O not detected).

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