

Application of the Novel Tandem Process *Diels-Alder Reaction/Ireland-Claisen Rearrangement* to the Synthesis of *rac*-Juvabione and *rac*-Epijuabione

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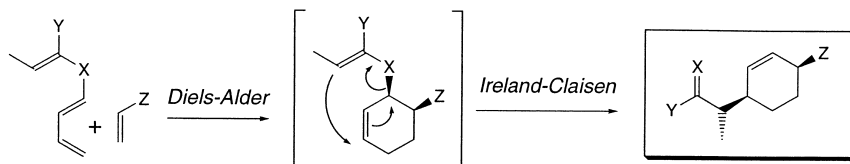
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Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

The novel tandem process *Diels-Alder reaction/Ireland-Claisen* rearrangement shows a high diastereoselectivity for the *Ireland-Claisen* rearrangement starting from the *endo*-product of the *Diels-Alder* reaction. Based on this mechanistic knowledge, the novel tandem process could be applied to the synthesis of *rac*-juvabione.

Introduction. – The length of a synthesis is determined by the increase of complexity achieved per synthetic operation. Combining several transformations into a one-pot reaction has proven to be one of the best strategies to increase the efficiency of organic synthesis [1]. Developing novel tandem reactions [2], also called domino reactions [3] or cascade reactions [4], has steadily gained in importance in recent years [5]. The combination of two stereoselective reactions like the *Diels-Alder* reaction and a sigmatropic rearrangement into one single synthetic operation can lead to interesting novel transformations [3b]. The individual steps have been known for a long time, and they are well-behaved so that the outcome of the tandem process can be predicted with confidence [6]. Our group has demonstrated the importance of the tandem reaction combining a cycloaddition with a [3,3]-sigmatropic rearrangement [7]. In an extension of our initial trials, we planned to combine the *Diels-Alder* cycloaddition with an *aza-Cope* rearrangement¹⁾, which, in this context, is also called *Ireland-Claisen* rearrangement (*Scheme 1*).

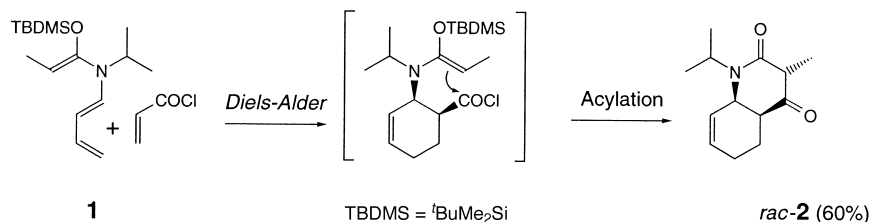
Scheme 1



¹⁾ The [3,3]-sigmatropic rearrangements, where N–C bonds are broken, are often called *aza-Cope* rearrangements [8]. However, the variants of the *Ireland-Claisen* rearrangements, where one of the O-atoms is replaced by an N-atom, are usually called *Eschenmoser* rearrangements [9], if the exocyclic O-atom is replaced, or *aza-Claisen* rearrangement [10] if the endocyclic O-atom is replaced.

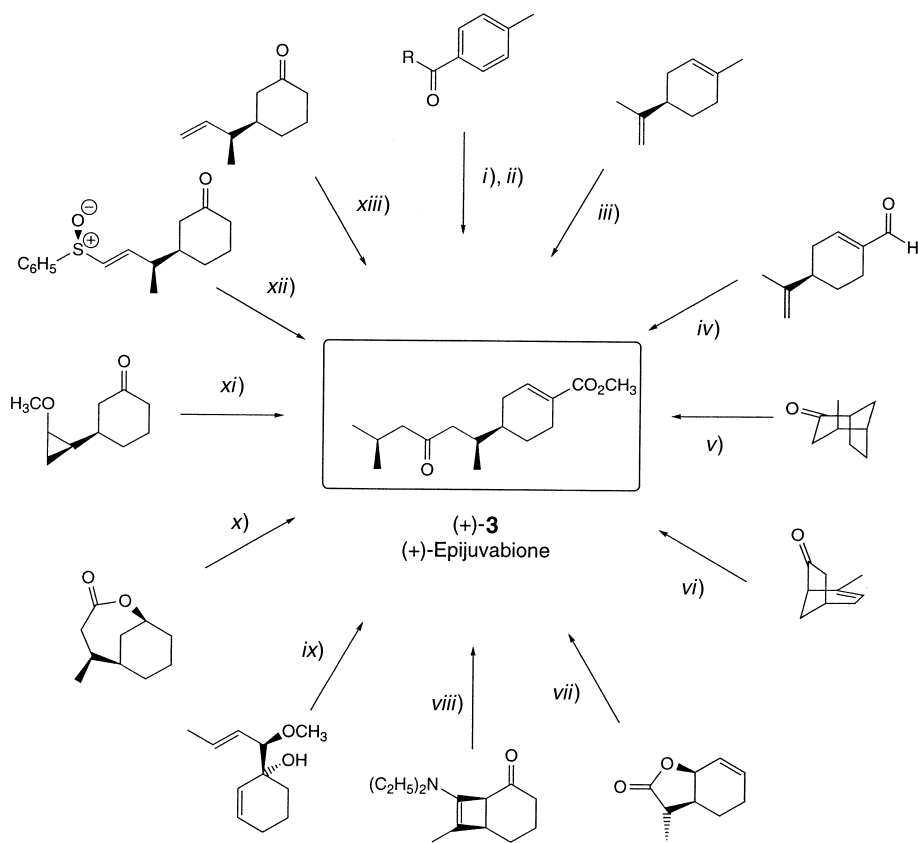
Looking for dienes that can be applied in this tandem reaction, we have synthesized a series of *N*-alkyl-*N*-butadienyl-*O*-(trialkylsilyl)-substituted ketene *N,O*-acetals of propanamide [7b][11]. If these dienes, e.g. **1**, would undergo a *Diels-Alder* reaction followed by the *aza-Cope* rearrangement, a total of three C–C bonds would be formed in one single transformation. The relative configuration of the two chiral centers at the ring-fusion site as well as the relative configuration of the third chiral C-atom would be controlled. Thereby, the increase in complexity that can be reached in one single step would be maximized. A series of differently *N*-alkyl-*N*-butadienyl-*O*-silyl-substituted ketene *N,O*-acetals of type **1** were treated with highly activated dienophiles like acryloyl chloride (*Scheme 2*). The bicyclic product *rac*-**2** (*Scheme 2*) was obtained as the result of an unexpected *Diels-Alder* cycloaddition/acylation process. The *aza-Cope* rearrangements require reaction temperatures of 135 to 150° [7b][11][12] and, therefore, the alternative process, the intramolecular acylation reaction is preferred. We have not been able to isolate products derived from a tandem process invoking a [3,3]-sigmatropic rearrangement (*Scheme 2*).

Scheme 2. *Diels-Alder Reaction/Acylation Tandem Process of the Ketene N,O-Acetal 1*



The *Ireland-Claisen* rearrangement of *O*-allyl-substituted ketene *O,O*-acetals can be brought about at considerably lower temperatures [13]. Therefore, we decided to develop a synthetic access to substituted *O*-butadienyl-*O*-(trialkylsilyl)substituted ketene *O,O*-acetals of acetic acid and to study their reactivity in the reaction sequence *Diels-Alder* reaction/*Ireland-Claisen* rearrangement [14]. (+)-Juvabione ((+)-**8**) is a sesquiterpene-derived cyclohexenecarboxylate isolated from balsam plants [15]. The assignment of the relative configuration to the natural product has been confusing. In the period between 1968 and 1976, all the structures of (+)-juvabione ((+)-**8**) and (+)-epijuvabione ((+)-**3**) have been reversed [16]. However, (+)-juvabione ((+)-**8**) as well as (+)-epijuvabione ((+)-**3**) have been isolated from natural sources. Juvabione (**8**) can modify the process of metamorphosis in insects and shows, therefore, juvenile hormone activity. Juvabione (**8**) has been synthesized at least 15 times [16][17]. If partial syntheses are counted as well, over 20 syntheses have been reported. Syntheses leading to mixtures of the diastereoisomers [18], syntheses leading to one pure diastereoisomer in racemic form [19], and syntheses leading to one enantiomer [20] have been reported (*Scheme 3*). The overall yields range from 0.4 to 53%. The number of steps necessary for the synthesis are in the range from 7 to 17, depending on the precursor used.

The synthesis from limonene as elaborate starting material requires only very few steps to furnish the natural product [18d][20e]. The shortest and most efficient synthesis of all, however, has been reported by *Negishi* and *Sabanski* starting from perillartine, which contains already the adequately functionalized cyclohexene-ring

Scheme 3. Starting Materials for the Known Synthesis of Epijuabione (**3**) and of Juvabione (**8**)

i) Synthesis by *Mori and Matsui* [18a]. ii) Synthesis by *Ayyar and Rao* [18b]. iii) Synthesis by *Trost and Tamatu* [18d] and by *Fuganti and Serra* [20e]. Limonene was also used as starting material by *Pawson* and co-workers to determine the absolute configuration of (+)-juvabione [20a]. iv) Shortest synthesis reported, by *Negishi and Sabanski* [18c]. v) Enantioselective synthesis by *Ogasawara* and co-workers [20d,f]. vi) Synthesis by *Larsen and Monti* [19a]. vii) Enantioselective synthesis by *Nagano and Mori* [20b]. viii) Synthesis by *Ficini* and co-workers [19b]. ix) Synthesis by *Evans and Nelson* [19c]. x) Synthesis by *Schultz and Dittami* [19e]. xi) Synthesis by *Morgans and Feigelson* [19d]. xii) Enantioselective synthesis by *Mori* and co-workers [20c]. xiii) Synthesis by *Tokoroyama and Pan* [18e].

skeleton [18c]; perillartine can be modified by the addition of one isoprene unit and the change of the oxidation state of the aldehyde group. The major challenge in these syntheses is the control of the relative configuration of the exocyclic chiral C-atom. Many of the diastereoselective syntheses have solved this problem by means of a classical approach [19b,e][20b,d,f]. A bicyclic intermediate was used to control the relative configuration. A ring-opening process allowed then formation of the product in a diastereoselective manner. In the context of our own studies, the application of the oxy-*Cope* rearrangement by the *Evans* group has to be mentioned [19c]. Only one of the reported synthesis [19a] involves the construction of the six-membered ring from

acyclic starting materials. All the other syntheses introduce the ring by means of an adequately substituted cyclic starting material.

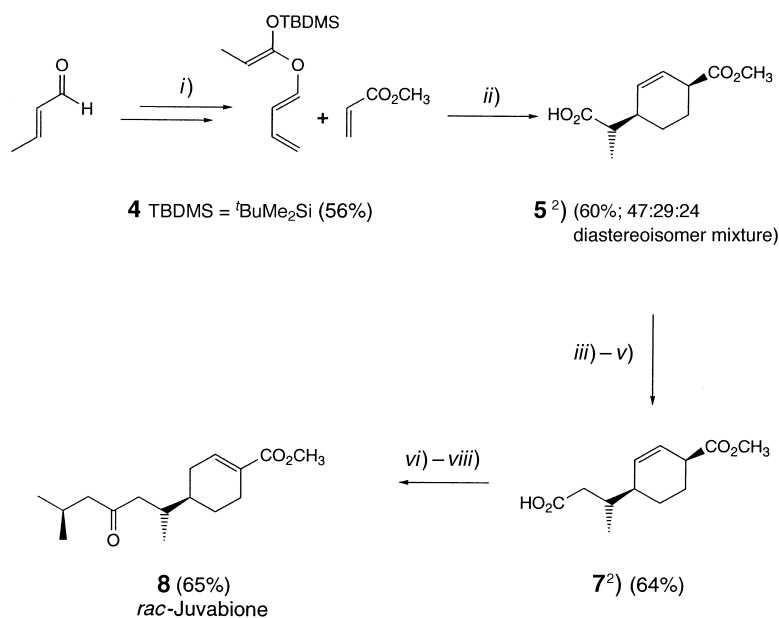
We report the application of our novel tandem reaction to the synthesis of *rac*-juvabione (**8**) starting from four acyclic precursors. *rac*-Juvabione (**8**) was obtained in 14% overall yield in 7 steps by our tandem reaction, which allowed the construction of the six-membered ring and the control of the relative configuration at the exocyclic chiral C-atom. This natural-product synthesis illustrates the synthetic potential of the tandem process.

Results and Discussion. – The diene **4** used for the *Diels-Alder* reaction/*Ireland-Claisen* rearrangement was prepared as described earlier [21]. Based on the method of *DeCusati* and *Olofson*, the (*E*)-isomer of buta-1,3-dien-1-yl propanoate was obtained in 66% yield starting from crotonaldehyde ((*E*)-but-2-enal) and propanoyl chloride [22]. The experimentally most delicate step was the transformation of the buta-1,3-dien-1-yl propanoate into the ketene acetal **4**. The reaction temperature had to be kept below -110° , otherwise only products derived from the known fragmentation process of ketene O,O-acetal to the butadienolate and the corresponding ketene could be detected [23]. To guarantee a high diastereoselectivity for the deprotonation and to obtain a sufficient reactivity of the ketene O,O-acetal towards the trapping agent, we had to use hexamethylphosphoric triamide (HMPA) or 3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one (DMPU) as cosolvent. Applying the *in situ* quench methodology with $t\text{BuMe}_2\text{SiCl}$ furnished the (*Z*)-ketene acetal **4** in a reproducible 83–84% yield (*Scheme 4*) [21]. The relative configuration could be determined by the analysis of the coupling constants and with the help of a NOESY experiment.

The ketene acetal **4** underwent the desired reaction sequence *Diels-Alder* reaction/*Ireland-Claisen* rearrangement under mild conditions (*Scheme 4*). Thus, heating **4** to 140° for 4 h in the presence of a ten-fold excess of methyl acrylate (methyl prop-2-enoate) as solvent and as dienophile and of a small amount of hydroquinone as inhibitor gave a good yield of the tandem product. Excess methyl acrylate was evaporated and the crude $t\text{BuMe}_2\text{Si}$ ester hydrolyzed with H_2SiF_6 solution (25 mol-%) [24]. After chromatography, the pure carboxylic acid **5** was obtained in 60% overall yield from **4** as a mixture of three diastereoisomers (ratio 47:29:24). Thus, an average yield of 85% for each of the three steps was achieved. The individual diastereoisomers were characterized by comparison of their ^1H - and ^{13}C -NMR spectra with the data obtained for the corresponding esters [21] and their structure confirmed by iodolactonization (*Scheme 5*) [25]. Thus, treatment of a hydrogen carbonate solution of the mixture **5** in MeCN with I_2 gave the iodolactone mixture in 71% yield, from which the major diastereoisomer **6** was isolated in 40% yield after flash chromatography. The X-ray analysis of **6** (see *Fig.*) allowed us to deduce the relative configuration of the major diastereoisomer of **5**. The major diastereoisomer of **5** was formed as a consequence of an *endo*-selective *Diels-Alder* reaction followed by a suprafacial *Ireland-Claisen* rearrangement involving a boat-like transition state [26].

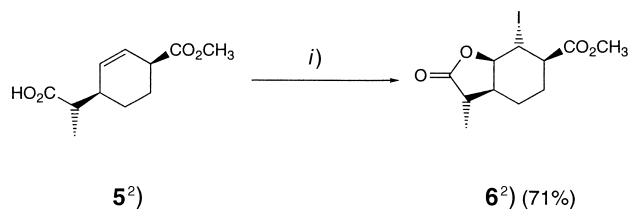
Carboxylic acid **5** was then homologated *via* the *Arndt-Eistert* reaction [27]. Treatment of the acid chloride (obtained *in situ* by reaction with oxalyl chloride) with diazomethane yielded the diazo ketone in 80% yield. The diazo ketone was rearranged to the homologous carboxylic acid **7** in 80% yield in the presence of silver trifluoroacetate as

Scheme 4



i) KO^tBu, THF, –78°, EtCOCl; NaHMDS (sodium hexamethyldisilazane), ^tBuMe₂SiCl THF/MeTHF 2 : 1, 10% DMPU, –110°. *ii*) 140°, 4 h; H₂SiF₆, (CH₂OMe)₂, 1 h. *iii*) (COCl)₂, CH₂Cl₂, r.t., 4 h. *iv*) CH₂Cl₂, THF; **5** → diazo ketone (80%). *v*) Ag(CF₃CO₂), 10% H₂O in THF, –25° → r.t., 4 h. *vi*) DBU, CH₂Cl₂, r.t., 24 h; **7** → conjugated ester (87%). *vii*) (COCl)₂, C₆H₆, r.t., 4 h. *viii*) 3%-mol [Fe(acac)₃], THF, C₄H₉MgBr, 0° → r.t., 15 min.

Scheme 5



i) I₂, NaHCO₃, MeCN, 0°, 3 h.

catalyst. On treatment²⁾ of **7** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature for 24 h, the corresponding conjugated ester was formed in 87% yield as low-melting 80:20 mixture of the two diastereoisomers. The final transformation into *rac*-juvabione (**8**) and *rac*-epijuvabione (**3**) needed some optimization. In our hands, the best way to introduce the missing isobutyl moiety was to add the commercially available isobutylmagnesium bromide in the presence of tris(acetylacetonato)iron(III) as catalyst at 0° according to the procedure of *Marchese* and co-workers [28]. After

²⁾ The major diastereoisomer is shown.

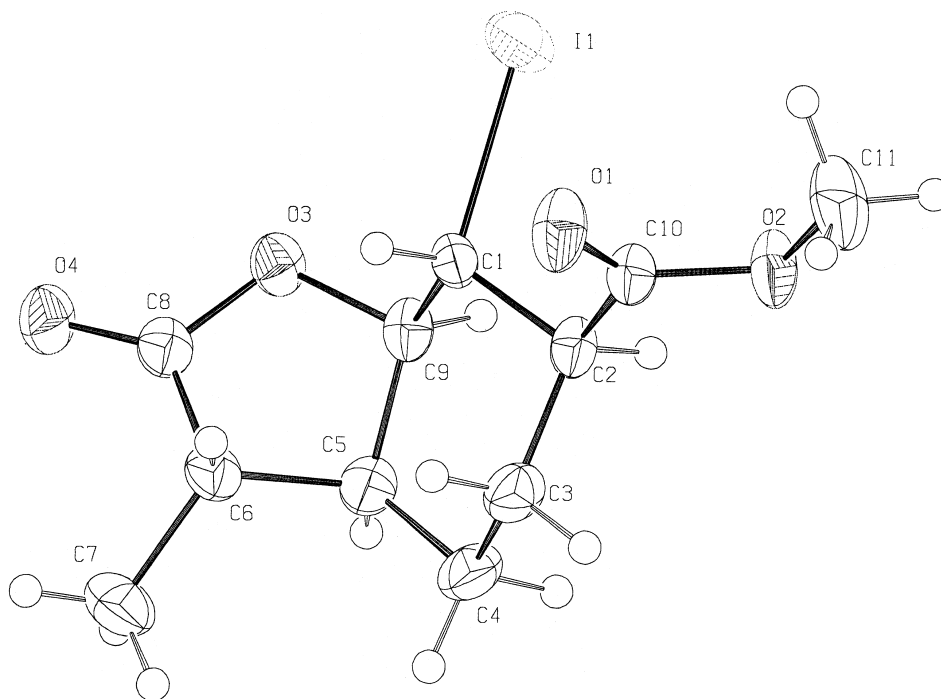


Figure. Perspective view [29] of molecule **6**, showing the crystallographic numbering scheme and the thermal ellipsoids at 50% probability level

flash chromatography, a 75% yield of the mixture of *rac*-juvabione (**8**) and *rac*-epijuvabione (**3**) was obtained. The spectra were identical with those kindly made available to us by *Fuganti* and *Serra* (cf. [20e]).

Conclusions. – Our novel tandem reaction was successfully applied to the synthesis of *rac*-juvabione (**8**) and *rac*-epijuvabione (**3**) in 14% overall yield starting from crotonaldehyde. Only the synthesis reported by *Trost* and *Tamatu* [18d] and *Negishi* and *Sabanski* [18c] starting from an elaborate natural product have reported a higher yield. The described tandem process requires only seven steps and is, together with the synthesis reported by *Negishi* and *Sabanski*, the shortest synthesis of the pheromones **3** and **8**. Three steps are necessary to construct the adequately substituted cyclohexene ring. The increased efficiency due to the application of the tandem reaction is nicely illustrated by the fact that the natural product is produced in only 4 further steps. This approach should also be amenable to the enantioselective synthesis of (+)-juvabione ((+)-**8**) and (+)-epijuvabione ((+)-**3**).

NMR Spectra (400 MHz) were measured by *Heinz Bursian* and Dr. *Saturnin Claude*, mass spectra by Dr. *Guy-Marie Dubin*, *Armelle Michel*, and *Christine Poliart*, and high-resolution mass spectra by *Fredy Nydegger* of the University of Fribourg. We thank the University of Neuchâtel and the *Swiss National Science Foundation* for support of this work.

Experimental Part

General. All moisture-sensitive reactions were carried out under Ar or N₂ using oven-dried glassware. All reagents were of commercial quality if not specifically mentioned. Solvents were freshly distilled prior to use. Flash chromatography (FC): Merck silica gel 60, 230–400 mesh; under positive pressure, 0.5–0.9 bar. TLC: precoated silica gel thin-layer sheets 60 F 254 from Merck, detection by UV or/and basic KMnO₄ soln. M.p.: Gallenkamp MFB-595; uncorrected. IR Spectra: Perkin Elmer FT-IR 1720 X; film on KBr; in cm⁻¹. NMR Spectra: Bruker AMX-400 (400 and 100 MHz) or Varian Gemini XL-2000 (200 and 50 MHz), at r.t., if not specified; chemical shifts δ in ppm rel. to SiMe₄ (=0 ppm) as internal reference; coupling constants J in Hz. MS: Nermag RC 30-10; EI, 70 eV; DCl, NH₄⁺. ESI-MS: Finnigan LCQ. HR-MS: Bruker FTMS 4.7T BioAPEXII.

(1*E*)-Buta-1,3-dien-1-yl Propanoate. Dist. crotonaldehyde (4.14 g, 60 mmol) was added dropwise within 10 min to a mechanically stirred soln. of KO^tBu (8 g, 71 mmol) in THF (40 ml) at –78° under N₂. After 10 min (→ yellow enolate), a soln. of propanoyl chlorid (6.8 g, 73 mmol) in THF (10 ml) was added within 10 min (→ orange-red, then orange). After 15 min stirring at –78°, the cooling bath was removed, the reaction quenched with H₂O, and the mixture extracted with Et₂O (3 × 50 ml). The extracts were washed with Na₂CO₃ (3 × 10 ml), NH₄Cl (3 × 10 ml), and NaCl soln. (3 × 10 ml), dried (Na₂SO₄) and evaporated. The crude oil was distilled: 4.98 g (66%) of pure butadienyl propanoate. Clear liquid. B.p. 50°/14 Torr. R_f (hexane/Et₂O 2:1) 0.58. IR: 3090w, 2986w, 2945w, 2886vw, 1762s, 1658m, 1464w, 1421m, 1360m, 1270w, 1232m, 1153s, 1114m, 1086m, 997m, 974w, 925w, 904w, 877w, 806w, 790w. ¹H-NMR (400 MHz, CDCl₃): 7.40 (*dq*, ³ $J(1', 2') = 12.4$, ⁴ $J(1', 3') \approx$ ⁵ $J(1', 4'a) \approx$ ⁵ $J(1', 4'b) = 0.7$, H–C(1')); 6.26 (*dddd*, ³ $J(3', 4'b) = 16.9$, ³ $J(3', 2') = 11.0$, ³ $J(3', 4'a) = 10.3$, ⁴ $J(3', 1') = 0.6$, H–C(3')); 6.01 (*ddt*, ³ $J(2', 1') = 12.4$, ³ $J(2', 3') = 11$, ⁴ $J(2', 4'a) \approx$ ⁴ $J(2', 4'b) = 0.7$, H–C(2')); 5.18 (*ddt*, ² $J(4'b, 4'a) = 1.6$, ⁴ $J(4'b, 3') = 16.9$, ⁴ $J(4'b, 2') \approx$ ⁵ $J(4'b, 1') = 0.8$, H_b–C(4')); 5.05 (*ddt*, ³ $J(4'a, 3') = 10.3$, ² $J(4'a, 4'b) = 1.6$, ⁴ $J(4'a, 2') \approx$ ⁵ $J(4'b, 1') = 0.7$, H_a–C(4')); 2.40 (*q*, ³ $J(2, 3) = 7.5$, CH₂(2)); 1.16 (*d*, ³ $J(3, 2) = 7.5$, Me(3)). ¹³C-NMR (100 MHz, CDCl₃): 171.2 (C(1)); 138.7 (C(1')); 131.7 (C(3')); 116.9 (C(4')); 115.8 (C(2')); 27.2 (C(2)); 8.7 (C(3)). EI-MS (70 eV): 126 (34, M⁺), 97 (2), 86 (21), 84 (35), 70 (16), 69 (11), 57 (100), 51 (11), 49 (29). HR-MS: 126.0675294 (M⁺; calc. 126.0676400).

(1*E*)-1-[(1*Z*)-1-[(*tert*-Butyl)dimethylsilyloxy]prop-1-enyl]oxybuta-1,3-diene (**4**). Procedure A. To 1*N* LHMDs/THF (20 ml, 20 mmol) in tetrahydro-2-methylfuran (MeTHF; 15 ml) at –60°, HMPA (dist. over Na; 6.5 ml) was rapidly added under mechanical stirring, followed by ^tBuMe₂SiCl (3 g, 15 mmol) in THF (10 ml). The yellow soln. was cooled to –110° (EtOH, N₂), and (1*E*)-buta-1,3-dien-1-yl propanoate (1.89 g, 15 mmol) in THF/Me THF 2:1 (15 ml) was added within 10 min, keeping the temp. below –110° to avoid decomposition of the ketene acetal enolate. The mixture was then stirred 1.5 h at ca. –115°. The reaction was quenched at ca. –115° with NH₄Cl soln. (30 ml) or 2*M* NaH₂PO₄ (30 ml), the mixture poured in pentane (150 ml), and the aq. phase extracted with pentane (3 × 150 ml). The extracts were washed with NH₄Cl (3 × 30 ml) and NaCl soln. (3 × 30 ml), dried (Na₂SO₄), and evaporated. The crude yellow oil was distilled: 2.98 g (83%) of **4**. Clear liquid.

Procedure B. As described in Procedure A, with 1*N* NaHMDS instead of LHMDs and DMPU (6 ml) instead of HMPA: 3.02 g (84%) of **4**. Clear liquid. B.p. 53°/0.06 mbar. R_f (hexane/Et₂O 2:1) 0.7. IR: 3091w, 3048vw, 2959m, 2931s, 2887w, 2861m, 1692s, 1657s, 1605vw, 1473w, 1464w, 1418w, 1389m, 1363w, 1338s, 1290w, 1256s, 1195s, 1174s, 1153s, 1095m, 1055s, 993m, 919m, 906m, 842s, 824m, 810s, 787s. ¹H-NMR (400 MHz, CDCl₃): 6.49 (*dd* (only two signals of the 'q' are resolved), ³ $J(1, 2) = 12.1$, ⁴ $J(1, 3) \approx$ ⁵ $J(1, 4a) \approx$ ⁵ $J(1, 4b) = 0.6$, H–C(1)); 6.23 (*dddd*, ³ $J(3, 4b) = 16.9$, ³ $J(3, 2) = 11.0$, ³ $J(3, 4a) = 10.3$, ⁴ $J(3, 1) = 0.6$, H–C(3)); 5.83 (*ddt*, ³ $J(2, 1) = 12.1$, ³ $J(2, 3) = 11$, ⁴ $J(2, 4a) \approx$ ⁴ $J(2, 4b) = 0.7$, H–C(2)); 5.09 (*ddt*, ² $J(4b, 4a) = 1.7$, ³ $J(4b, 3) = 16.9$, ⁴ $J(4b, 2) \approx$ ⁵ $J(4b, 1) = 0.7$, H_b–C(4)); 4.93 (*ddt*, ² $J(4a, 4b) = 1.7$, ³ $J(4a, 3) = 10.3$, ⁴ $J(4a, 2) \approx$ ⁵ $J(4b, 1) = 0.6$, H_a–C(4)); 3.81 (*q*, ³ $J(2', 3') = 6.6$, H–C(2')); 1.52 (*d*, ³ $J(3', 2') = 6.6$, Me(3')); 0.95 (*s*, ^tBuSi); 0.17 (*s*, Me₂Si). ¹³C-NMR (100 MHz, CDCl₃): 154.0 (C(1')); 145.1 (C(1)); 132.2 (C(3)); 114.2 (C(4)); 113.4 (C(2)); 78.0 (C(2')); 25.6 (Me₃CSi); 18.0 (Me₂CSi); 9.6 (C(3')); –4.4 (Me₂Si). EI-MS (70 eV): 240 (1.4, M⁺), 183 (11), 115 (17), 75 (19), 74 (29), 73 (100), 59 (32), 45 (25). Anal. calc. for C₁₃H₂₄O₂Si: C 64.95, H 10.06; found: C 64.92, H 10.09.

4-(Methoxycarbonyl)-*a*-methylcyclohex-2-ene-1-acetic Acid (**5**). Methyl acrylate (5 ml, 50 mmol) was added under Ar to **4** (1.2 g, 5 mmol) and hydroquinone (85 mg, 1 mmol). The mixture was sealed in a tube and heated at 140° (oil bath) for 4 h. After cooling to r.t., the excess methyl acrylate was evaporated, and (CH₂OMe)₂ (15 ml) and 25% aq. H₂SiF₆ soln. (1 ml, 1.5 mmol) were added. The mixture was stirred at r.t. for 1 h. (CH₂OMe)₂ was evaporated, the crude mixture dissolved in THF (2 ml), poured into Et₂O (100 ml), and washed with sat. NaHCO₃ soln. (3 × 20 ml). The aq. phase was carefully acidified at 0° to pH ≈ 2 with conc. HCl soln. and extracted with Et₂O (3 × 100 ml). The org. phase was dried (Na₂SO₄) and evaporated. Purification by FC (hexane/AcOEt 6:4) gave **5** (646 mg, 60%) as a mixture of three diastereoisomers in a ratio of 47:29:24 by

¹H-NMR, signals of H–C(2) and H–C(3)). Colorless oil. IR: 3037m, 2951s, 2871m, 2643w, 1734vs, 1705vs, 1513w, 1455m, 1436m, 1384m, 1289m, 1265m, 1202s, 1180s, 1155s, 1103w, 1089w, 1075w, 1036m, 1006w, 970w, 949w, 935w, 899w, 868w, 848w, 832w, 790w, 759vw, 731m, 684w, 639w, 568vw. ¹H-NMR (400 MHz, CDCl₃): major (47%) isomer (±)-*rel* (αR,1S,4R) **5**: 5.85 (dm, ³J(2,3) = 10.2, H–C(3)); 5.71 (dm, ³J(2,3) = 10.2, H–C(2)); 3.70 (s, COOMe); 3.09–3.06 (m, H–C(4)); 2.70–2.37 (m, H–C(α), H–C(1)); 2.11–2.07 (m, H_a–C(5)); 1.79–1.68 (m, H_b–C(5)); 1.57–1.48 (m, H_a–C(6)); 1.79–1.68 (m, H_b–C(6)); 1.15 (d, ³J(Me,α) = 6.8, Me–C(α)). ¹³C-NMR (100 MHz, CDCl₃): 182.6 (COOH); 174.7 (COOMe); 132.4 (C(2)); 126.0 (C(3)); 52.3 (COOMe); 40.4 (C(4)); 44.1 (C(α)); 37.7 (C(1)); 23.9 (C(5)); 22.5 (C(6)); 13.7 (Me–C(α)); minor (29%) isomer (±)-*rel* (αR,1S,4S) **5**: 5.85 (dm, ³J(2,3) = 10.2, H–C(3)); 5.67 (d^m, H–C(2)); 3.71 (s, COOMe); 3.40–3.10 (m, H–C(4)); 2.70–2.37 (m, H–C(α), H–C(1)); 2.11–2.07 (m, H_a–C(5)); 1.79–1.68 (m, H_b–C(5)); 1.47–1.33 (m, H_a–C(6)); 1.91–1.80 (m, H_b–C(6)); 1.14 (d, ³J(Me,α) = 6.8, Me–C(α)). ¹³C-NMR (100 MHz, CDCl₃): 182.3 (COOH); 175.1 (COOMe); 131.7 (C(2)); 126.5 (C(3)); 52.4 (COOMe); 44.14 (C(α)); 42.0 (C(4)); 38.1 (C(1)); 25.4 (C(5)); 24.5 (C(6)); 13.4 (Me–C(α)); minor (24%) isomer (±)-*rel* (αR,1R,4R) **5**: 5.85 (dm, ³J(2,3) = 10.2, H–C(3)); 5.78 (dm, ³J(2,3) = 10.2, H–C(2)); 3.71 (s, COOMe); 3.40–3.10 (m, H–C(4)); 2.70–2.37 (m, H–C(α), H–C(1)); 2.11–2.07 (m, H_a–C(5)); 1.79–1.68 (m, H_b–C(5)); 1.47–1.33 (m, H_a–C(6)); 1.91–1.80 (m, H_b–C(6)); 1.18 (d, ³J(Me,α) = 6.8, Me–C(α)). ¹³C-NMR (100 MHz, CDCl₃): 182.4 (COOH); 175.1 (COOMe); 130.5 (C(2)); 126.7 (C(3)); 52.4 (COOMe); 44.0 (C(α)); 42.0 (C(4)); 38.1 (C(1)); 26.3 (C(6)); 25.3 (C(5)); 13.8 (Me–C(α)). ESI-MS: 212.9 ([M + H]⁺). HR-MS: 235.0940350 ([M + Na]⁺); calc. 235.094074).

Methyl 4-(3-Diazo-1-methyl-2-oxopropyl)cyclohex-2-ene-1-carboxylate. To a soln. of **5** (1.750 g, 8.2 mmol) in dry CH₂Cl₂ (20 ml), abs. DMF (1–2 drops) was added and the mixture cooled to 0°. Oxalyl chloride (1.275 g, 10 mmol) was slowly added, and after 10 min, the cooling bath was removed and the mixture stirred for 4 h at r.t. Excess oxalyl chloride and solvent were evaporated. Dry THF (15 ml) was added and the mixture treated with ca. 0.3M CH₂N₂ soln. in Et₂O (ca. 100 ml) until the yellow color of CH₂N₂ persisted. The mixture was stirred overnight at r.t. The excess of CH₂N₂ was destroyed by vigorous stirring. The org. soln. was washed with sat. NH₄Cl soln. (15 ml) and NaCl soln. (15 ml), dried (Na₂SO₄) and evaporated and the yellow oil purified by FC (hexane/AcOEt 8:2): 1.56 g (80%) of pure diazo ketone as an isomer mixture 44:35:21 by ¹³C-NMR. Yellow oil. R_f (hexane/AcOEt 6:4) 0.51. IR: 3091m, 3029m, 2951s, 2868m, 2104vs, 1735vs, 1637vs, 1511w, 1449s, 1435s, 1366vs, 1322s, 1260s, 1197s, 1171s, 1033s, 930m, 902m, 865w, 831w, 817w, 784w, 729m, 693w, 572w, 519m, 501w, 493m, 442w. ¹H-NMR (400 MHz, CDCl₃): major (44%) (±)-*rel* (1R,1'R,4S)-isomer: 5.82 (dm, ³J(2,3) = 10.2, H–C(2)); 5.72–5.62 (dm, ³J(2,3) = 10.2, H–C(3)); 5.29 (br. s, H–C(4)); 3.69 (s, COOMe); 3.08–3.06 (m, H–C(1)); 2.68–2.40 (m, H–C(1')); 2.29–2.21 (m, H–C(4)); 2.11–2.01 (m, H_a–C(6)); 1.78–1.67 (m, H_b–C(6)); 1.53–1.41 (m, H_a–C(5)); 1.78–1.67 (m, H_b–C(5)); 1.11 (d, ³J(Me,1') = 6.7, Me–C(1')). ¹³C-NMR (100 MHz, CDCl₃): 198.6 (C(2')); 174.8 (COOMe); 132.7 (C(3)); 125.6 (C(2)); 54.9 (C(3')); 52.2 (COOMe); 49.7 (C(4)); 40.6 (C(1)); 38.1 (C(1')); 23.8 (C(6)); 23.2 (C(5)); 14.8 (Me–C(1')); minor (35%) (±)-*rel* (1R,1'S,4R)-isomer: 5.82 (dm, ³J(2,3) = 10.2, H–C(2)); 5.72–5.62 (dm, ³J(2,3) = 10.2, H–C(3)); 5.29 (br. s, H–C(3')); 3.70 (s, COOMe); 3.12–3.10 (m, H–C(1)); 2.68–2.40 (m, H–C(1')); 2.29–2.21 (m, H–C(4)); 2.11–2.01 (m, H–C(6)); 1.78–1.67 (m, H_b–C(6)); 1.40–1.24 (m, H_a–C(5)); 1.89–1.85 (m, H_b–C(5)); 1.10 (d, ³J(Me,1') = 6.9, Me–C(1')). ¹³C-NMR (100 MHz, CDCl₃): 198.2 (C(2')); 175.0 (COOMe); 131.9 (C(3)); 126.2 (C(2)); 54.9 (C(3')); 52.3 (COOMe); 49.7 (C(4)); 42.0 (C(1)); 38.5 (C(1')); 25.3 (C(6)); 25.0 (C(5)); 14.1 (Me–C(1')). Minor (21%) *rel* (1R,1'R,4R)-isomer: 5.82 (dm, ³J(2,3) = 10.2, H–C(2)); 5.72–5.62 (dm, ³J(2,3) = 10.2, H–C(3)); 5.29 (br. s, H–C(3')); 3.70 (s, COOMe); 3.12–3.10 (m, H–C(1)); 2.68–2.40 (m, H–C(1')); 2.29–2.21 (m, H–C(4)); 2.11–2.01 (m, H_a–C(6)); 1.78–1.67 (m, H_b–C(6)); 1.40–1.24 (m, H_a–C(5)); 1.89–1.85 (m, H_b–C(5)); 1.14 (d, ³J(Me,1') = 6.8, Me–C(1')). ¹³C-NMR (100 MHz, CDCl₃): 198.1 (C(2')); 175.0 (COOMe); 130.8 (C(3)); 126.6 (C(2)); 54.9 (C(3')); 52.3 (COOMe); 49.7 (C(4)); 42.0 (C(1)); 38.6 (C(1')); 26.5 (C(5)); 25.3 (C(6)); 14.5 (Me–C(1')). ESI-MS: 237.0 ([M + H]⁺). HR-MS: 259.1053320 ([M + Na]⁺); calc. 259.1053084).

4-(Methoxycarbonyl)-β-methylcyclohex-2-ene-1-propanoic Acid (7). A soln. of the diazo ketone mixture (1.51 g, 6.4 mmol) in THF (25 ml) containing 10% of H₂O was cooled to –25° (bath temp.) and treated with a soln. of CF₃CO₂Ag (174 mg, 0.8 mmol, 0.12 equiv.) in Et₃N (1.88 g, 18.6 mmol, 2.9 equiv.) under Ar and exclusion of light. The mixture was allowed to warm to r.t. during 4 h in the dark, then diluted with Et₂O, and extracted with sat. NaHCO₃ soln. The aq. phase was carefully adjusted at 0° to pH 2–3 with HCl soln. and extracted with Et₂O. The org. phase was dried (Na₂SO₄) and evaporated: 1.56 g (80%) of sufficiently pure crude **7** as an isomer mixture 48:32:20 (by ¹³C-NMR). Pale yellow oil. An anal. sample was obtained by FC (hexane/AcOEt 6:4). IR: 3030m, 2952s, 2870m, 2647w, 1737vs, 1707vs, 1450m, 1436m, 1418m, 1383m, 1284m, 1205s, 1173s, 1074m, 1036m, 947w, 905w, 866w, 845w, 785w, 756w, 729m, 691w, 545vw, 493vw. ¹H-NMR (400 MHz,

CDCl₃): 5.84 (*dm*, ³*J*(2,3) = 10.2, H–C(3)); 5.72 (*dm*, ³*J*(2,3) = 10.2, H–C(2)); 3.70 (*s*, COOMe); 3.14–3.07 (*m*, H–C(4)); 2.23–2.06 (*m*, H–C(1)); 2.18 (*dd*, ²*J*(*aa,ab*) = 15.0, ³*J*(*aa,β*) = 8.9, H_a–C(*α*)); 2.45 (*dd*, ²*J*(*ab,αα*) = 15.0, ³*J*(*ab,β*) = 5.0, H_b–C(*α*)); 2.23–2.06 (*m*, H–C(β)); 2.23–2.06 (*m*, H_a–C(5)); 1.25–1.59 (*m*, H_b–C(5)); 1.25–1.59 (*m*, H_a–C(6)); 1.53 (*ddd*(*m*), ²*J*(6a,6b) = 12.6, ³*J*(6b,5b) = 9.5, ³*J*(6b,5a) = 3.0, H_b–C(6)); 0.95 (*d*, ³*J*(Me,β) = 6.7, Me–C(β)). ¹³C-NMR (100 MHz, CDCl₃): major (48%) (±)-*rel*-(β*R*,1*R*,4*S*)-**7**: 179.6 (COOH); 174.5 (COOMe); 132.8 (C(2)); 125.2 (C(3)); 51.8 (COOMe); 40.0 (C(4)); 39.3 (C(1)); 38.6 (C(*α*)); 33.9 (C(β)); 23.9 (C(5)); 21.4 (C(6)); 16.2 (Me–C(β)); minor (32%) (±)-*rel*-(β*R*,1*R*,4*R*)-**7**: 179.5 (COOH); 175.0 (COOMe); 132.1 (C(2)); 125.7 (C(3)); 51.9 (COOMe); 41.9 (C(4)); 39.4 (C(1)); 38.5 (C(*α*)); 33.9 (C(β)); 25.3 (C(5)); 23.4 (C(6)); 16.0 (Me–C(β)); minor (20%) (±)-*rel*-(β*R*,1*S*,4*S*)-**7**: 179.5 (COOH); 171.4 (COOMe); 131.6 (C(2)); 126.1 (C(3)); 51.8 (COOMe); 42.0 (C(4)); 40.9 (C(1)); 38.0 (C(*α*)); 33.8 (C(β)); 25.5 (C(5)); 24.4 (C(6)); 16.7 (Me–C(β)). ESI-MS: 225.5 ([*M* – H][–]). HR-MS: 249.1098170 ([*M* + Na]⁺; calc. 249.1097244).

4-(Methoxycarbonyl)-β-methylcyclohex-3-ene-1-propanoic Acid. To a stirred soln. of mixture **7** (400 mg, 1.77 mmol) in dry CH₂Cl₂ (6 ml), DBU (2.5 ml, 16.4 mmol) was added. The mixture was stirred at r.t. for 24 h, poured into CH₂Cl₂ (10 ml), and washed with 10% HCl soln. (3 × 10 ml), the org. phase dried (Na₂SO₄) and evaporated, and the crude product purified by FC (silica gel, CH₂Cl₂/AcOEt 6:4): conjugated ester (351 mg, 87%), which crystallized at 4° as a diastereoisomer mixture 78:22 (by ¹H- and ¹³C-NMR). Colorless oil. IR: 3200*m*, 2928*s*, 2256*vw*, 1712*vs*, 1651*s*, 1437*s*, 1384*s*, 1256*vs*, 1214*s*, 1161*s*, 1084*s*, 1047*m*, 1034*m*, 995*m*, 923*m*, 805*m*, 732*m*, 715*m*, 495*w*. ¹H-NMR (400 MHz, CDCl₃): 6.97 (*dt*, ³*J*(2,3) = 5.2, ⁴*J*(1,3) ≈ ⁴*J*(3,5) = 2.5, H–C(3)); 3.74 (*s*, COOMe); 2.53–2.45 (*m*, H_b–C(5)); 2.48 (*dd*, ²*J*(*aa,ab*) = 15.1, ³*J*(*aa,β*) = 5.2, H_a–C(*α*)); 2.30–2.12 (*m*, H_a–C(2), H_a–C(5)); 2.21 (*dd*, ²*J*(*ab,αα*) = 15.1, ³*J*(*ab,β*) = 8.9, H_b–C(*α*)); 2.06–1.91 (*m*, H_b–C(2), H–C(β)); 1.85 (*ddq*, ²*J*(6a,6b) = 12.8, ³*J*(6a,5a) = 5.5, ⁴*J*(6a,5b) = 2.3, H_a–C(6)); 1.56–1.48 (*m*, H–C(1)); 1.23 (*dq*, ²*J*(6b,6a) = 12.6, ³*J*(6b,5a) = 5.2, H_b–C(6)); 1.0 (*d*, ³*J*(Me,β) = 6.8, Me–C(β)). ¹³C-NMR (100 MHz, CDCl₃): 179.8 (COOH); 168.3 (COOMe); 139.5 (C(3)); 130.6 (C(4)); 52.0 (COOMe); 39.2 (C(*α*)); 37.9 (C(1)); 34.4 (C(β)); 30.1 (C(2)); 25.1 (C(5)); 25.0 (C(6)); 16.8 (Me–C(β)). ESI-MS: 225.8 ([*M* – H][–]). HR-MS: 249.1095870 ([*M* + Na]⁺; calc. 249.1097244).

Methyl (±)-*rel*-(4*R*)-4-[*(1R)*-1,5-Dimethyl-3-oxohexyl]cyclohex-1-enecarboxylate (= *rac*-Juvabione; **8**). To a stirred soln. of **11** the conjugated-ester mixture 78:22 (160 mg, 0.7 mmol) in dry benzene (3 ml), oxalyl chloride (280 mg, 2.20 mmol) was added at 0°. After 15 min, the cooling bath was removed and the mixture stirred 4 h at r.t. The excess oxalyl chloride and the solvent were evaporated and the resulting crude mixture dissolved in THF (5 ml). Tris(acetylacetonato)iron(III) (8 mg, 0.022 mmol, 3 mol-%) was added, the mixture cooled to 0°, and 2*M* isobutylmagnesium bromide/THF (0.35 ml, 0.7 mmol) added dropwise (15 min) under N₂. Stirring was continued for 15 min at 0° and for 15 min at r.t. The reaction was quenched with 10% aq. HCl soln., the mixture extracted with several portions of Et₂O, the combined Et₂O extract washed with NaHCO₃ soln. and H₂O, dried (Na₂SO₄) and evaporated and the yellow oily residue purified by FC (hexane/AcOEt 95:5): 141 mg (75%) of **8/3** in a ratio 80:20 (by ¹H- and ¹³C-NMR) or 88:12 (by GC). Colorless oil.

Data of **8**: *R*_f (hexane/AcOEt 9:1) 0.3. IR: 2956*s*, 2873*m*, 1713*s*, 1652*m*, 1436*m*, 1411*m*, 1383*m*, 1368*m*, 1332*w*, 1312*m*, 1255*s*, 1213*m*, 1190*m*, 1171*m*, 1084*s*, 1035*m*, 946*w*, 924*w*, 804*w*, 745*w*, 714*w*, 504*w*. ¹H-NMR (400 MHz, CDCl₃): 6.97 (*dd*, ³*J*(2,3) = 5.1, ⁴*J* = 2.4, H–C(2)); 3.74 (*s*, COOMe); 2.51 (*br. d*, ²*J*(6b,6a) = 17.2, H_b–C(6)); 2.46 (*dd*, ²*J*(2'a,2'b) = 16.1, ³*J*(2'a,1') = 4.7, H_a–C(2')); 2.31 (*d*, ³*J*(4',5') = 6.9, CH₂(4')); 2.26 (*dd*, ²*J*(2'b,2'a) = 16.1, ³*J*(2'b,1') = 8.8, H_b–C(2')); 2.29–1.91 (*m*, CH₂(3), H_a–C(6), H–C(1'), H–C(5')); 1.81 (*ddd*(*d*), ²*J*(5a,5b) = 12.7, ³*J*(5a,4) = 5.2, ³*J*(5a,6) = 2.2, H_a–C(5)); 1.46 (*m*, H–C(4)); 1.23 (*qd*, ²*J*(5b,6a) = 12.3, ³*J*(5b,4) ≈ ³*J*(5b,6) = 5.1, H_b–C(5')); 0.94 (*d*, ³*J*(6',5') = 6.5, Me(6')); 0.93 (*d*, ³*J*(Me,5') = 6.5, Me–C(5')); 0.90 (*d*, ³*J*(Me,1') = 6.8, Me–C(1')). ¹³C-NMR (100 MHz, CDCl₃): 210.5 (C(3')); 167.8 (COOMe); 139.3 (C(2)); 130.1 (C(1)); 52.4 (C(4')); 51.5 (COOMe); 47.7 (C(2')); 37.7 (C(4)); 32.6 (C(5')); 29.7 (C(3)); 24.8 (C(6)); 24.6 (C(5)); 24.5 (C(1')); 22.6 (Me–C(5')); 22.5 (Me(6')); 16.4 (Me–C(1')). ESI-MS: 289.2 ([*M* + Na]⁺). HR-MS: 289.1772460 ([*M* + Na]⁺; calc. 289.1774104).

Methyl (±)-*rel*-(3*R*,3*A*R,6*S*,7*S*,7*A*S)-Octahydro-7-iodo-3-methyl-2-oxobenzofuran-6-carboxylate (**6**). To a stirred soln. of diastereoisomer mixture **5** (160 mg, 0.75 mmol) in MeCN (3.6 ml), NaHCO₃ (2.61 g, 31 mmol) was added. This mixture was cooled to 0°, and I₂ (795 mg, 3.1 mmol) was added in one portion. The mixture was stirred for 3 h at 0°. Then Et₂O (20 ml) was added, the org. phase washed with sat. Na₂S₂O₃ soln. (until complete decoloration) and sat. NaCl soln., dried (Na₂SO₄), and evaporated, and the crude product (180 mg, 71%) purified by FC (hexane/AcOEt 8:2): 101 mg (40%) of the major isomer **6**. White crystals. M.p. = 148°. IR: 2986*m*, 2934*s*, 2874*m*, 2046*w*, 1777*vs*, 1741*vs*, 1450*s*, 1383*s*, 1336*m*, 1294*s*, 1259*s*, 1243*s*, 1201*s*, 1174*vs*, 1156*vs*, 1112*s*, 1072*s*, 1029*s*, 1001*vs*, 968*s*, 918*s*, 898*m*, 867*m*, 835*w*, 812*m*, 761*vw*, 731*m*, 696*m*, 642*m*, 597*m*, 547*m*, 507*vw*, 484*vw*. ¹H-NMR (400 MHz, CDCl₃): 4.76 (*dd*, ³*J*(7a,7) = 9.8, ³*J*(7a,3a) = 7.3, H–C(7a)); 4.04 (*dd*, ³*J*(7,7a) = 9.8,

$^3J(7,6) = 12.1$, $H-C(7)$; 3.78 (*s*, COOMe); 2.87 (*td*, $^3J(6,7) = 12.0$, $^3J(6,5b) = 3.1$, $H-C(6)$); 2.59 (*dq*, $^3J(\text{Me},3) = 6.8$, $^3J(3,3a) = 13.1$, $H-C(3)$); 2.28 (*ddd*, $^3J(3a,\text{Me}) = 13.1$, $^3J(3a,7a) \approx 6.6$, $^3J(3a, 4ax) \approx 1.8$, $H-C(3a)$); 2.06–2.00 (*m*, $H_{\text{eq}}-C(4)$); 1.92–1.82 (*m*, $H_{\text{ax}}-C(4)$, $H_{\text{ax}}-C(5)$); 1.64 (*qd*, $^3J(5_{\text{eq}},5_{\text{ax}}) = 11.6$, $^3J(5_{\text{eq}},4_{\text{ax}}) = 3.9$, $H_{\text{eq}}-C(5)$); 1.25 (*d*, $^3J(\text{Me}, 3) = 6.9$, $\text{Me}-C(3)$). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 177.5 (C(2)); 172.5 (COOMe); 82.2 (C(7a)); 52.4 (COOMe); 51.3 (C(6)); 43.2 (C(3a)); 35.0 (C(3)); 27.6 (C(7)); 25.5 (C(5)); 23.0 (C(4)); 13.0 (*Me-C(3)*). ESI-MS: 339.1 ($[M+H]^+$). HR-MS: 360.9903800 ($[M+Na]^+$; calc. 360.9907224).

Crystal-Structure Determination of 6. Crystal Data. $\text{C}_{11}\text{H}_{15}\text{IO}_4$, M_r 338.13, triclinic, $P(\text{No. } 2)$, $T = 223(2)\text{K}$; $a = 7.283(1)$, $b = 9.304(2)$, $c = 10.382(2)$ Å $\alpha = 101.20(2)$, $\beta = 99.04(2)$, $\gamma = 110.83(2)^\circ$; $V = 625.0(2)$ Å³, $Z = 2$, $D_x = 1.797$ g·cm⁻³; 4650 reflections measured, 2325 independent reflections ($R_{\text{int}} = 0.017$) used in the structure solution and refinement; 2154 observed reflections ($I > 2\sigma(I)$), absorption coefficient $\mu = 2.559$ mm⁻¹.

Data Collection and Processing. Suitable crystals were grown from CH_2Cl_2 and $^3\text{Pr}_2\text{O}$; colorless blocks. Intensity data were collected for a crystal of dimensions $0.38 \times 0.27 \times 0.19$ mm at 223(2)K on a *Stoe-AED2*-4-circle diffractometer by means of MoK_α graphite-monochromated radiation ($\lambda 0.71073$ Å) with $\omega/2\theta$ scans in the θ range 2–25.5°. Two standard reflections were measured every hour, and the data were corrected for an overall decay of 3%. No suitable ψ scans could be measured, and the application of an empirical absorption correction, using DIFABS [29], did not improve the R_{int} value; hence, no absorption correction was applied.

Structure Analysis and Refinement. The structure was solved by direct methods with the program SHELXS-97 [30]. The refinement and all further calculations were carried out with SHELXL-97 [31]. The H-atoms were located from difference maps and refined isotropically. The non-H-atoms were refined anisotropically by weighted full-matrix least-squares on F^2 . Final $R_1 = 0.0223$, $wR = 0.0525$ (observed data), goodness of fit 1.126, residual density max/min 0.618/–0.482 eÅ⁻³. Crystallographic data (excluding structure factors) for structure **6** has been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication no. CCDC-144604. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

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