# Synthesis of Bicyclic Homochiral Dienes by Allylic Rearrangement of Cyclohexenols – Suitable Building Blocks for the Synthesis of Nagilactones

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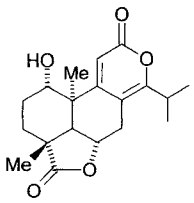
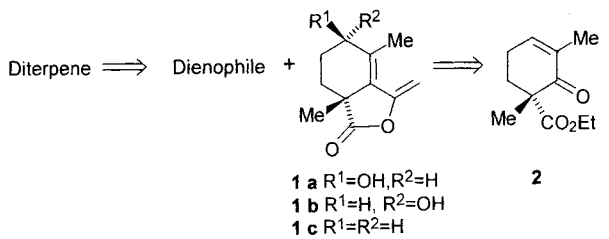
A very short and straightforward synthesis towards highly functionalized dienes is described. The homochiral starting material, unsaturated β-oxo ester **2**, can be prepared by enzyme-catalyzed saponification. The utility of the dienes has been demonstrated in a cycloaddition with *N*-phenyltriazolidinone as the dienophile. The Diels-Alder reaction is highly diastereoselective, yielding only one diastereomer.

Diels-Alder reactions are widely used for the synthesis of carbocyclic products due to their high regio- and stereoselectivity[1–6]. Of particular interest is the use of conformationally restricted chiral dienes, since they offer high and predictable diastereofacial control. This has been demonstrated by carbohydrate-based dienes[7] and by vinyl-substituted cyclohexenes bearing a quaternary centre at the allylic position[8]. Even more restricted dienes are bicyclic lactones such as **1**. The butadienes **1** are fixed in the *s-cis* conformation with the methyl group covering the *convex* site of the fused bicyclic ring system. Furthermore, the chiral quaternary centre should govern the stereochemical outcome of cycloaddition reactions utilizing appropriate dienophiles.

Scheme 1




Nagilactone A




**1 a** $R^1$=OH,$R^2$=H
**1 b** $R^1$=H, $R^2$=OH
**1 c** $R^1$=$R^2$=H

**2**

Lactones **1** can been regarded as suitable precursors for the synthesis of nagilactone-type diterpenoides. Nagilactones (e.g. nagilactone A) are members of an important class of natural products. They can be isolated from the seeds and bark of *Podocarpus nagi* and show biological activity as antitumor agents, plant growth promoters and insect larvae toxins[9].

In continuation of our studies concerning the synthesis of homochiral building blocks bearing a chiral quaternary carbon centre[10], we were interested in the synthesis of precursors such as **1**. Due to the hydroxy group at C-4, dienes **1a, b** offer the unprecedented opportunity to synthesize nagilactones with a hydroxy-functionalized A-ring, a goal which has not previously been achieved[9]. In this paper we report on a straightforward and convenient route for the synthesis of these dienes and on their Diels-Alder reactions with 4-phenyl-1,2,4-triazolin-3,5-dione (PTAD).

## Results and Discussion

As outlined in the retrosynthetic analysis (Scheme 1) unsaturated β-oxo esters such as **2** are suitable starting materials for the synthesis of dienes **1**. Precursors for the synthesis of **2** are α-methylated β-oxo valerates **3** which undergo a tandem Michael/aldol reaction upon addition of acrolein. To obtain β-oxo ester **2** in an optically pure state, the racemate was resolved by pig liver esterase (PLE) catalyzed saponifications. Racemic β-oxo ester (±)-**2** was hydrolyzed with high stereoselectivity allowing the isolation of optically pure (−)-**2**; the corresponding β-oxo acid (+)-**2** underwent decarboxylation and racemization during the enzymatic reaction and work-up to yield **4**. The enantiomeric excess of (−)-**2** was determined to be >99% by GLC using a cyclodextrin-modified stationary phase (LIPODEX E®[11]). The configuration at the stereogenic centre was determined to be (*R*), as was established by chemical correlation. Enamino esters derived from β-oxo esters and (*S*)-1-phenylethylamine undergo Michael reactions predominantely by *si* approach to an α,β-unsaturated system yielding

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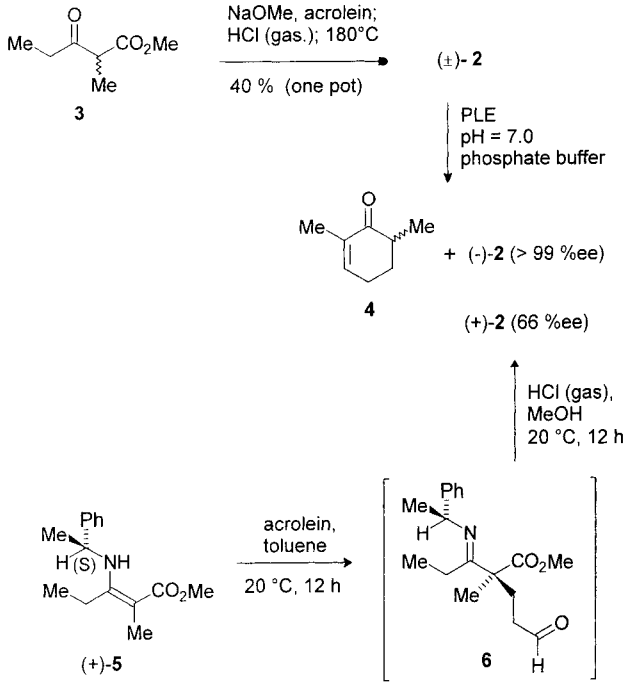
(*S*)-configured quaternary carbon centres as the main products[12]. Michael addition of enamino ester (+)-**5** with acrolein and subsequent aldol condensation was carried out by a similar procedure to that described for (±)-**2**. The *ee* value of (+)-**2** provided by this latter method was determined to be 66%; in this case, the GLC retention times of the major and minor enantiomers were reversed.

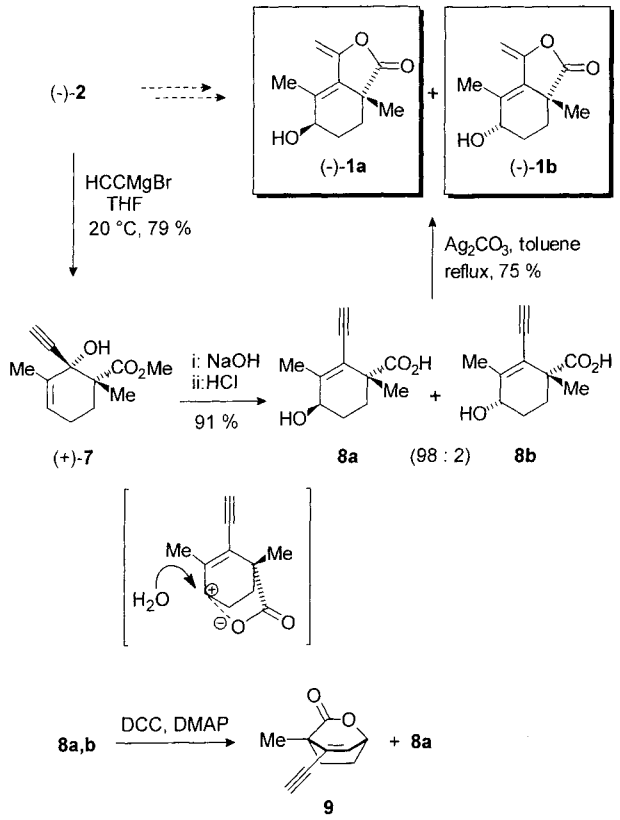
Scheme 2




The first step towards the synthesis of diene **1** was the incorporation of a C-2 building block into β-oxo ester **2** (Scheme 3). This was easily achieved by nucleophilic addition with magnesium acetylide to afford **7** in high yield (79%). The alkynylation is highly diastereoselective (96:4, GLC), and it can be assumed that the major diastereomer results from an axial attack of the nucleophile at the carbonyl group[13]. The product should exhibit a *cis* configuration of the hydroxy and the carboxyl moieties.

The next key step towards the synthesis of dienes **1** was the formal rearrangement of the allylic alcohol **7** to enyne **8**[14]. To obtain the rearranged product **8**, allylic alcohol **7** was first saponified and then stirred for 30 min in the presence of HCl. After this short period, TLC analysis indicated complete consumption of the starting material, and the desired enyne **8** could be isolated in almost quantitative yield (91%). The diastereomeric ratio of the resulting allylic alcohol was 98:2 (**8a**:**8b**) as determined by GLC. The two diastereomeric alcohols were inseparable by other chromatographic methods, and so **8a** had to be purified by repeated crystallization. To verify the structures of the two diastereomeric alcohols, both **8a** and **8b** were subjected to lactonization with DCC in the presence of DMAP. The minor diastereomer was cyclized to lactone **9**, whereas the major diastereomer was left unchanged. The structural assign-

Scheme 3



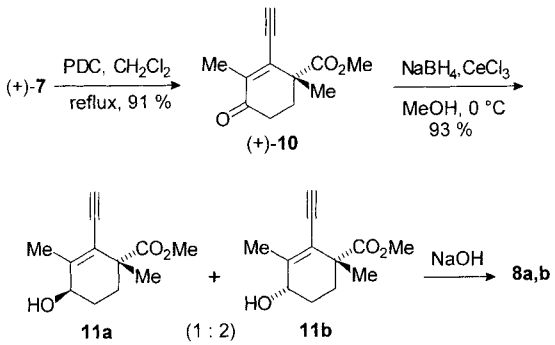

ments could thus be confirmed as a 1,4-*trans* configuration for the major diastereomer **8a** and a 1,4-*cis* configuration for the minor component **8b**. We assume that the highly diastereoselective allylic rearrangement was supported by a 1,4-neighbouring effect induced by the carboxylate moiety, as indicated in Scheme 3, although no lactone was formed as an intermediate. The synthetic route used, i.e. saponification followed by rearrangement, is advantageous over the alternative route in which the rearrangement is carried out primarily by treatment of the allylic alcohol **7** with acid. In the latter, the diastereomeric ratio of the products formed is only 85:15 (**11a**/**11b**), and furthermore, unwanted by-products are formed.

Subsequent cyclization of the acid **8** to the diene **1** was carried out in the presence of a catalytic amount of $Ag_2CO_3$[15]. Lactone **1** was formed through a 5-*exo*-*dig* ring closure; no product formed by a 6-*endo*-*dig* process could be observed. Diene **1a** was isolated in a yield of 75%, accompanied by traces of **1b** owing to the presence of **8b**. At this stage of the synthesis, the diastereomeric alcohols **1a** and **1b** could easily be separated by crystallization or by chromatography. In this very short and efficient synthesis, diene (−)-**1a** was obtained in a three-step procedure starting from enantiomerically pure **2** in an overall yield of 52%.

In order to obtain the epimeric diene **1b** as the main component, a slightly different approach was used (Scheme 4). Starting from the propargylic alcohol **7**, an oxidative allylic rearrangement[16] was carried out using two equivalents of

PDC in boiling $CH_2Cl_2$. After 7 h, the resulting cyclohexenone **10** could be obtained in an excellent yield of 91%. Subsequent reduction led to the unseparable alcohols **11a** and **11b** in quantitative yield. Unfortunately, only a low diastereoselectivity could be achieved, despite trying a variety of complex hydrides. The best result, a 1 : 2 ratio of the corresponding alcohols, was obtained by using the Luche reagent in MeOH/$H_2O$ (1 : 1) at 0 °C[17]. The major diastereomer was the *cis*-configured allylic alcohol **11b**. Subsequent saponification of **11** was carried out easily, and lactonization of the resulting acid **8** to the corresponding dienes **1a** and **1b** was achieved using $Ag_2CO_3$ (Scheme 3). Reduction at a later stage of the synthesis could not be carried out, since **10** decomposes upon treatment with base. Utilizing this protocol, diene **1b** was synthesized in a five-step procedure in an overall yield of 33% starting from homochiral (−)-**2**.

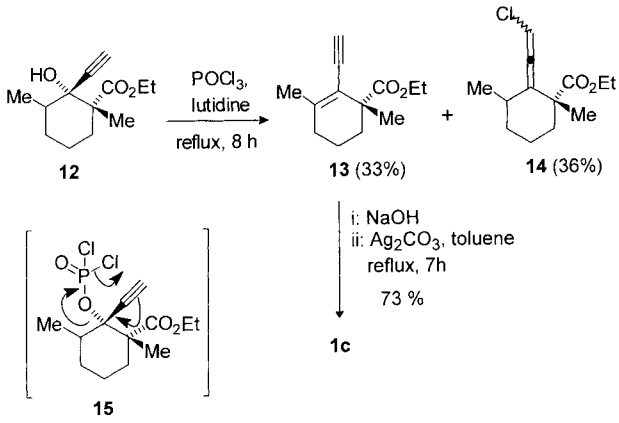
Scheme 4



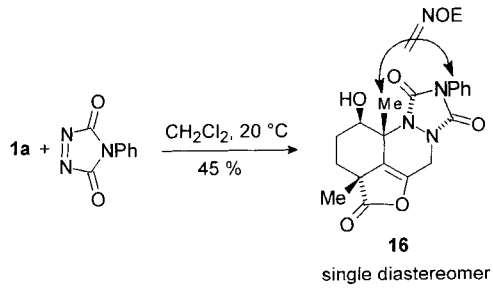

Initial attempts to synthesize deoxy diene **1c** according to the route outlined in Scheme 5 met with only moderate success. Elimination of the tertiary hydroxy group has proven to be troublesome. In order to obtain **13** through dehydration of **12**, $POCl_3$ and high-boiling lutidine as solvent had to be used. Enyne **13** was isolated in 33% yield, along with another product, determined to be allene **14**, which was formed in 36% yield. The formation of allene **14** can be explained by the intermediate **15** formed with $POCl_3$. The use of low-boiling pyridine and similar solvents led to even higher yields of allene **14**. The synthesis of **1c** was carried out as described for **8** (Scheme 3), furnishing the diene in 24% yield starting from **12**.

To demonstrate the reactivity of dienes **1** in [4 + 2] cycloadditions, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) was utilized as the dienophile, with **1a** as the diene (Scheme 6). The Diels-Alder reaction of diene **1a** with PTAD could be accomplished at 20 °C to afford the desired cycloadduct in 45% yield after 10 min. The cycloadduct **16** was formed as a single diastereomer and its structure was revealed by 1- and 2D-NMR experiments. No olefinic protons could be observed in the $^1$H-NMR spectrum, whereas the $^{13}$C-NMR spectrum clearly indicated the presence of two olefinic carbons at δ = 119.8 and 130.7, respectively, showing no $^{13}$C-NMR multiplicities in the DEPT-135 spectrum. By using PTAD no discussion of whether *endo* or *exo* attack occurred has to be taken into account, solely the question concerning the configuration at the newly formed stereogenic center remains unsolved. For steric reasons we assume that attack of the dienophile PTAD should be opposite to the methyl group at the quaternary centre of the diene. Therefore, the two methyl groups should be *cis*-configured. This structural assumption is supplemented by the fact that no NOE between the methyl group and the phenyl moiety of the dienophile could be observed (Scheme 6)[18]. This is in agreement with the proposed stereochemical outcome of this Diels-Alder reaction.

Scheme 5




Scheme 6




In summary, the synthesis of conformationally restricted homochiral dienes **1a**–**c** has been accomplished by very short and efficient reaction sequences. Cycloaddition of **1a** with PTAD leads to diastereomerically pure **16**, demonstrating the high diastereofacial selectivity using these dienes.

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## Experimental Section

All air- and moisture-sensitive reactions were performed under argon using oven-dried glassware. All solvents were dried with standard drying agents; THF was used freshly distilled from sodium. Enzymic reactions were monitored using a Methrom 702 SM Ti-

trino titrator; chiral GLC was performed with a Lipodex E column (12 m)[11]. Pig liver esterase was purchased from Sigma. Reactions were monitored by TLC on silica gel 60 $F_{254}$. Column chromatography was performed on silica gel 60 (70–230 mesh, ASTM). M.p.s were determined with a Gallenkamp melting point apparatus in open capillaries and are uncorrected. Optical rotations were measured in solution at 589 nm with a Perkin-Elmer 241 polarimeter using a 1.00-dm cell. $^1$H-(200 MHz) and $^{13}$C-(50 MHz) NMR spectra were recorded with a Bruker AMX-200 with TMS as internal standard. All coupling constants $J$ are given in Hz; the carbon multiplicities were assigned by DEPT-135 pulse-sequence techniques. IR spectra were recorded with a Nicolet 510 FT-IR spectrometer and GC-MS analysis was performed with a Finnigan MAT magnum System 240, Varian GC 3400 DB 5. Elemental analyses were carried out with a Perkin-Elmer Elemental Analyzer 240 at this university.

*(−)-(1R)-Methyl 1,3-Dimethyl-2-oxocyclohex-3-ene-1-carboxylate* (**2**): To a solution of sodium methoxide prepared from sodium (0.02 g, 0.9 mmol) and methanol (30 ml), methyl 2-methyl-3-oxovalerate (**3**) (3.42 g, 24.0 mmol) was added dropwise. After cooling in ice, freshly distilled acrolein (1.34 g, 24.0 mmol) in methanol (8 ml) was added dropwise and stirring was continued for about 12 h at 20 °C. The mixture was again cooled in ice and a passage of HCl (gas) was maintained until the colour changed to red (approx. 2–3 h). Stirring was continued for around a further 12 h at 20 °C and then the reaction mixture was filtered and evaporated to dryness. The dark brown residue was heated for 1 h at 180 °C (catalytic amount of hydroquinone) and purified by distillation under reduced pressure to give 1.70 g (40%) of (±)-**2**. The kinetic resolution was carried out as follows: To a phosphate buffer (0.1 M, $KH_2PO_4$/$K_2HPO_4$, 200 ml), was added (±)-**2** (1.50 g, 8.2 mmol) and PLE (100 µl) and the mixture was stirred at 20 °C. The pH was kept constant by periodic addition of NaOH (2 N). During the reaction, the *ee* values were monitored by GLC (Lipodex E). On completion of the reaction, the mixture was acidified with HCl (pH = 2) and extracted overnight with $Et_2O$. After drying of the organic layer, $MgSO_4$ was filtered off, the solvent was evaporated and the remaining oily residue was distilled in a Kugelrohr apparatus, to yield 590 mg (39%) of (−)-**2**. – B. p. 88 °C/1.1 Torr. – $[\alpha]_D^{20}$ = −81.2 (*c* = 1.55 in $CHCl_3$). – IR (film): $\tilde{\nu}$ = 2978 cm$^{-1}$, 2872, 1736, 1676. – $^1$H NMR ($CDCl_3$): δ = 1.27 (s, 3 H, $CH_3$), 1.70 (s, 3 H, $CH_3$), 1.68–1.85 (m, 1 H), 2.21–2.44 (m, 3 H), 3.59 (s, 3 H, $OCH_3$), 6.58 (dd, *J* = 3.2 Hz, 1 H, =CH). – $^{13}$C NMR ($CDCl_3$): δ = 16.7 (q), 20.6 (q), 23.6, 33.9 (2 t), 52.6 (q), 53.5 (s), 134.9 (s, =C), 144.5 (d, =CH), 173.6 (s, CO), 197.6 (s, CO). – GC-MS (80 eV); *m/z* (%): 182 (25), 167 (28), 150 (50), 135 (15), 123 (41), 95 (22), 82 (100), 79 (14). – $C_{10}H_{14}O_2$ (182.2): calcd. C 65.92, H 7.74; found C 65.78, H 7.75.

*(+)-(1R,2R)-Methyl 2-Ethynyl-2-hydroxy-1,3-dimethylcyclohex-3-ene-1-carboxylate* (**7**): To a solution of (−)-**2** (0.50 g, 2.75 mmol) in THF (5 ml) at 20 °C, ethynylmagnesium bromide [9.05 ml (0.5 M in THF), 4.53 mmol] was added dropwise over a period of 30 min. Stirring at this temperature was continued for 1 h, after which the reaction mixture was quenched by the addition of satd. aq. $NH_4Cl$ solution (3 ml). The organic layer was separated and the aqueous phase was extracted with $Et_2O$ (3 × 50 ml). The combined organic layers were washed with 10% HCl, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 9 : 1) to give 0.45 g (79%) of **7** as colourless crystals. $R_f$ = 0.21 (petroleum ether/ethyl acetate, 9 : 1). – M. p. 79.2 °C. – $[\alpha]_D^{20}$ = +232.4 (*c* = 1.17 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3478 cm$^{-1}$, 3244, 2980, 2959, 2933, 2100, 1705. – $^1$H NMR ($CDCl_3$): δ = 1.27 (s, 3 H, $CH_3$), 1.86 (s, 3 H, $CH_3$), 1.92–2.21 (m, 4 H, ≡CH), 3.78 (s, 3 H, $CH_3$), 4.11 (s, 1 H, OH), 5.43 (s, 1 H, =CH). – $^{13}$C NMR ($CDCl_3$): δ = 17.1 (q), 18.1 (q), 22.0 (t), 27.9 (t), 50.3 (s, C-1), 52.6 (q), 71.6 (s, C-2), 72.5 (d, C≡*C*H), 86.5 (s, *C*≡CH), 123.4 (d, =CH), 134.4 (s, =C), 178.2 (s, CO). – GC-MS (70 eV); *m/z* (%): 191 (12) [$M^+$ − OH], 175 (30), 147 (18), 131 (40), 107 (85), 91 (28), 79 (100). – $C_{12}H_{16}O_3$ (208.3): calcd. C 69.21, H 7.74; found C 69.05, H 7.91.

*(+)-(1R,4S)-2-Ethynyl-4-hydroxy-1,3-dimethylcyclohex-2-ene-1-carboxylic Acid* (**8a**): A solution of **7** (0.10 g, 0.48 mmol), NaOH (0.5 N, 5 ml) and methanol (3 ml) was stirred for 2 d. The mixture was then hydrolyzed with HCl (10%, 20 ml) and stirred for 30 min. Subsequently, the solution was extracted with $Et_2O$ (3 × 80 ml). The organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give 0.09 g (quant.) of **8a** as colourless crystals ($CH_2Cl_2$). – M. p. 158.3 °C. – $[\alpha]_D^{20}$ = +129.0 (*c* = 0.55 in $CHCl_3$/$CH_3OH$, 9 : 1). – IR (film): $\tilde{\nu}$ = 3410 cm$^{-1}$, 3298, 3057, 2984, 2945, 2876, 2100, 1790. – $^1$H NMR ($CDCl_3$): δ = 1.24–1.40 (m, 1 H), 1.50 (s, 3 H, $CH_3$), 1.70–2.08 (m, 3 H), 2.09 (s, 3 H, $CH_3$), 3.20 (s, 1 H, ≡CH), 4.15 (t, 1 H, 4-H), 5.88 (s, br., 2 H, OH and COOH). – $^{13}$C NMR ($CDCl_3$): δ = 19.9 (q), 24.8 (q), 28.5 (t), 30.2 (t), 46.6 (s, C-1), 68.3 (d, CHOH), 81.4 (s, *C*≡CH), 83.3 (d, C≡*C*H), 120.9 (s, =C), 145.6 (s, =C), 181.4 (s, COOH). – $C_{11}H_{14}O_3$ (194.2): calcd. C 68.02, H 7.27; found C 67.92, H 7.45.

*(−)-(5R,7aR)-* (**1a**) *and (−)-(5S,7aR)-5-Hydroxy-4,7a-dimethyl-3-methylene-5,6,7,7a-tetrahydroisobenzofuran-1-one* (**1b**): A flask containing a solution of **8** (0.73 g, 3.8 mmol) and $Ag_2CO_3$ (0.15 g, 0.54 mmol) in toluene was immersed in an oil bath preheated to 120 °C and the contents were refluxed for 1 h under argon. The mixture was filtered through Celite, which was washed with toluene, and the filtrate was concentrated under reduced pressure. The oily residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 2 : 1) to give 0.55 g (75%) of **1a** (**1b**: 8 mg) as a colourless oil. – **1a**: $R_f$ = 0.12 (petroleum ether/ethyl acetate, 2 : 1). – $[\alpha]_D^{20}$ = −64.2 (*c* = 1.27 in $CHCl_3$) – IR (film): $\tilde{\nu}$ = 3443 cm$^{-1}$, 3059, 2984, 2953, 1797, 1651. – $^1$H NMR ($CDCl_3$): δ = 1.27–2.23 (m, 5 H, $CH_2$, OH), 1.42 (s, 3 H, $CH_3$), 1.96 (s, 3 H, $CH_3$), 4.20 (t, 1 H, C*H*OH), 4.63 (d, *J* = 2.1 Hz, 1 H, =$CH_2$), 5.05 (d, *J* = 2.1 Hz, 1 H, =$CH_2$). – $^{13}$C NMR ($CDCl_3$): δ = 16.6 (q), 24.2 (q), 28.6 (t), 28.8 (t), 43.4 (s, C-7a), 72.3 (d, C-5), 93.2 (t, C=*C*$H_2$), 131.4 (s, =C), 135.9 (s, =C), 153.0 (s, =C), 177.8 (s, CO). – GC-MS (80 eV); *m/z* (%): 194 (42) [$M^+$], 166 (42), 147 (25), 133 (41), 122 (100), 105 (52), 91 (22), 79 (23). $C_{11}H_{14}O_3$ (194.2): calcd. C 68.02, H 7.27; found C 68.14, H 7.38.

**1b**: $R_f$ = 0.20. – $[\alpha]_D^{20}$ = −128 (*c* = 0.43 in $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3443 cm$^{-1}$, 3059, 2984, 2953, 1797, 1651. – $^1$H NMR ($CDCl_3$): δ = 1.31 (s, 3 H, $CH_3$), 1.73–1.78 (m, 2 H, $CH_2$), 1.94–2.05 (m, 2 H, $CH_2$), 1.98 (s, 3 H, $CH_3$), 2.34 (s, br., 1 H, OH), 4.11 (t, 1 H, C*H*OH), 4.63 (d, *J* = 2.4 Hz, 1 H, =$CH_2$), 5.04 (d, *J* = 2.4 Hz, 1 H, =$CH_2$). – $^{13}$C NMR ($CDCl_3$): δ = 16.8 (q), 22.9 (t), 23.2 (q), 27.6 (t), 43.5 (s, C-7a), 67.0 (d, C-5), 93.1 (t, C=*C*$H_2$), 131.1 (s, =C), 134.6 (s, =C), 153.2 (s, =C), 177.8 (s, CO). – GC-MS (80 eV); *m/z* (%): 195 (88) [$M^+$ + 1], 177 (50), 166 (28), 149 (22), 138 (68), 124 (82), 123 (100), 109 (44), 105 (48), 81 (42), 79 (38). $C_{11}H_{14}O_3$ (194.2): calcd. C 68.02, H 7.27; found C 67.91, H 7.45.

*5-Ethynyl-4-methyl-2-oxabicyclo[2.2.2]oct-5-ene-3-one* (**9**): M. p. 51.2 °C. – $R_f$ = 0.80 (petroleum ether/ethyl acetate, 1 : 1). – IR (KBr): $\tilde{\nu}$ = 2965 cm$^{-1}$, 2894, 1760. – $^1$H NMR ($CDCl_3$): δ = 1.52 (s, 3 H, $CH_3$), 1.56–1.78 (m, 3 H, $CH_2$), 2.08 (s, 3 H, $CH_3$), 2.16–2.32 (m, 1 H, $CH_2$), 3.38 (s, 1 H, ≡CH), 5.00 (dd, 1 H, *J* = 1.3, *J* = 1.1 Hz, CHOC). – $^{13}$C NMR ($CDCl_3$): δ = 17.5 (q), 17.9 (q), 26.1 (t), 28.7 (t), 44.8 (s), 78.1 (d, CHO), 83.1 (s, ≡C), 86.2 (d,

≡CH), 122.9 (s, =C), 147.6 (s, =C), 175.9 (s, CO) – GC-MS (80 eV); *m/z* (%): 176 [$M^+$] (5), 132 [$M^+ - CO_2$] (100), 117 (49), 115 (26), 91 (11), 63 (9).

*(+)-(1R)-Methyl 2-Ethynyl-1,3-dimethyl-4-oxocyclohex-2-ene-1-carboxylate* (**10**): PDC (0.72 g, 1.90 mmol) was added to a solution of **7** (0.20 g, 0.90 mmol) in absolute $CH_2Cl_2$ (5 ml), in the presence of a catalytic amount of hydroquinone. The suspension was refluxed under argon for 7 h. At the end of the reaction, ethyl acetate (1 ml) was added and the product was separated from the chromium salts by a short-column chromatography (silica gel, petroleum ether/ethyl acetate, 9:1) to give 0.18 g (91%) of **10**. (The product had to be stored in a freezer, otherwise polymerization occurred). – $R_f$ = 0.1 (petroleum ether/ethyl acetate, 9:1). – $[\alpha]_D^{20}$ = +48.4 (*c* = 0.98 in $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3262 $cm^{-1}$, 2984, 2955, 2100, 1736, 1674, 1593. – $^1H$ NMR ($CDCl_3$): δ = 1.57 (s, 3H, $CH_3$), 1.89–2.0 (m, 2H, $CH_2$), 2.03 (s, 3H, $CH_3$), 2.39–2.57 (m, 2H, $CH_2$), 2.50 (s, 1H, ≡CH), 3.76 (s, 3H, $OCH_3$). – $^{13}C$ NMR ($CDCl_3$): δ = 14.8 (q), 24.4 (q), 33.9, 34.7 (2 t), 47.5 (s), 53.0 (q), 80.6 (s, *C*≡CH), 92.5 (d, C≡*C*H), 138.2, 141.5 (2 s, C=C), 174.7 (s, CO), 197.4 (s, CO). – GC-MS (70 eV); *m/z* (%): 207 (100) [$M^+$], 191 (50), 178 (23), 150 (21), 119 (65), 91 (50). – $C_{12}H_{14}O_3$ (206.2): calcd. C 69.89, H 6.84; found C 69.72, H 7.03.

*(1R,4R)-Methyl 2-Ethynyl-4-hydroxy-1,3-dimethylcyclohex-2-ene-1-carboxylate* (**11a**), *(1R,4S)-Methyl 2-Ethynyl-4-hydroxy-1,3-dimethylcyclohex-2-ene-1-carboxylate* (**11b**): A mixture of $NaBH_4$ (0.04 g, 0.97 mmol) and $CeCl_3$ (0.02 g, 0.08 mmol) was added in portions to an ice-cooled solution of (+)-**10** (0.10 g, 0.48 mmol) in methanol/water (1:1, v/v, 5 ml) and the solution was stirred for 30 min. The reaction mixture was then hydrolyzed with water (20 ml) and extracted with $Et_2O$ (3 × 50 ml). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give 0.10 g (quant.) of **11a** and **11b** as an unseparable mixture of diastereomers (ratio **11a/11b** = 1:2). – IR (film): $\tilde{\nu}$ = 3431 $cm^{-1}$, 3300, 2984, 2949, 2874, 2100, 1728. – NMR spectra were taken from the diastereomeric mixture; signals attributable to the minor diastereomer **11a** are marked with an asterisk*: $^1H$ NMR ($CDCl_3$): δ = 1.39 (s, 3H, $CH_3$), 1.46* (s, 3H, $CH_3$), 1.49–2.23 (m, 8H, $CH_2$), 2.06 (s, 6H, $CH_3$), 2.42–2.54 (s, br., OH), 3.12 (s, 1H, ≡CH), 3.14* (s, 1H, ≡CH), 3.69* (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 4.03 (t, *J* = 5.2 Hz, 1H, C*H*OH), 4.11* (t. *J* = 4.2 Hz, 1H, C*H*OH). – $^{13}C$ NMR ($CDCl_3$): δ (**11b**, taken from the mixture of diastereomers) = 19.6 (q), 23.6 (q), 28.5 (t), 30.7 (q), 47.3 (s, C-1), 52.8 (q, $OCH_3$), 68.6 (d, C-4), 81.5 (s, *C*≡CH), 82.6 (d, C≡*C*H), 120.7 (s, =C), 145.8 (s, =C), 177.1 (s, CO). – $^{13}C$ NMR ($CDCl_3$): δ (**11a**, taken from the mixture of diastereomers) = 19.8 (s), 24.8 (q), 28.6 (t), 30.4 (t), 46.9 (s, C-1), 52.6 (q, $OCH_3$), 68.4 (d, C-4), 81.5 (s, *C*≡CH), 82.7 (d, C≡*C*H), 121.0 (s, =C), 145.5 (s, =C), 176.5 (s, CO). – GC-MS (80 eV); *m/z* (%, **11b**): 209 (12) [$M^+$ + 1], 193 (80), 191 (85), 180 (100), 165 (53), 149 (79), 148 (80), 133 (70), 131 (49), 115 (42), 107 (71), 105 (84), 91 (75), 79 (57). – GC-MS (80 eV); *m/z* (%, **11a**): 209 (16) [$M^+$ + 1], 193 (55), 191 (100), 180 (79), 165 (43), 149 (58), 133 (28), 105 (45), 91 (20), 79 (15). – $C_{12}H_{16}O_3$ (208.3): calcd. C 69.21, H 7.74; found C 69.04, H 7.77.

*Ethyl 2-Ethynyl-1,3-dimethylcyclohex-2-ene-1-carboxylate* (**13**) *and Ethyl 2-Chlorovinylidene-1,3-dimethylcyclohexane-1-carboxylate* (**14**): A solution of **12** (0.20 g, 0.88 mmol) and $POCl_3$ (0.16 ml, 0.16 mmol) in lutidine (4 ml) was refluxed for 16 h. After cooling to 0°C, HCl (10%, 10 ml) was added. The reaction mixture was then extracted with $Et_2O$ (4 × 50 ml) and the combined organic layers were washed with HCl (10%), water, brine, dried ($MgSO_4$) and concentrated. The oily residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 98:2) to afford 60 mg (33%) of **13** and 80 mg (36%) of **14**, which were formed as 1:1 mixtures of diastereomers. – **13**: $R_f$ = 0.20 (petroleum ether/ethyl acetate, 98:2). – IR (film): $\tilde{\nu}$ = 3277 $cm^{-1}$, 2980, 2937, 2870, 2828, 2100, 1728. – $^1H$ NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3H, $CH_2CH_3$), 1.43 (s, 3H, $CH_3$), 1.46–1.75 (m, 3H), 1.97 (s, 3H, $CH_3$), 2.02–2.22 (m, 3H), 3.07 (s, 1H, OH), 4.17 (q, *J* = 7.2 Hz, 2H, $OCH_2$). – $^{13}C$ NMR ($CDCl_3$): δ = 14.6 (q), 19.3 (t), 22.9 (q), 24.6 (q), 31.7, 34.5 (2 t), 46.5 (s), 61.1 (t), 80.9 (d, ≡CH), 82.4 (s, ≡C), 117.8 (s, =C), 145.4 (s, =C), 176.6 (s, CO). – GC-MS (70 eV); *m/z* (%): 206 (9) [$M^+$], 191 (25), 163 (25), 133 (100), 117 (52), 105 (70), 91 (55), 77 (30). – $C_{13}H_{18}O_2$ (206.3): calcd. C 75.69, H 8.80; found C 75.48, H 9.01. – **14**: $R_f$ = 0.30 (petroleum ether/ethyl acetate, 98:2). – IR (film): $\tilde{\nu}$ = 2961 $cm^{-1}$, 2932, 2872, 1975, 1732. – $^1H$ NMR ($CDCl_3$): δ = 0.91–0.99 (m, 1H), 1.08 (d, $^3J$ = 6.5 Hz, 3H, $CH_3$ at C-1), 1.26 (t, $^3J$ = 7.1 Hz, 3H, $CH_2CH_3$), 1.32 (s, 3H, $CH_3$ at C-3), 1.36–2.44 (m, 6H, 3 $CH_2$), 4.18 (q, $^3J$ = 7.1 Hz, 2H, $OCH_2$), 6.23, 6.25 (s, 1H, =CHCl, diastereomers). – $^{13}C$ NMR ($CDCl_3$): δ = 14.6 (q), 19.9 (q), 23.6 (t), 26.2 (q), 34.3 (d), 36.0 (t), 38.1 (t), 48.3 (s), 61.2 (s), 91.7 (d, CHCl), 124.9 (s, C-2), 175.5 (s, CO), 198.3 (s, =C=). – GC-MS (70 eV); *m/z* (%): 243 [$M^+$], 245 [$M^+$], 227 (100), 229 (32), 199 (88), 201 (27), 169 (75), 171 (23), 133 (89), 135 (29), 105 (79), 91 (83), 77 (38). – $C_{13}H_{19}O_2Cl$ (242.8): calcd. C 64.32, H 7.89; found C 64.14, H 8.03.

*4,7a-Dimethyl-3-methylene-5,6,7,7a-tetrahydroisobenzofuran-1-one* (**1c**): A solution of **13** (0.20 g, 1.0 mmol) in methanol (2 ml) and NaOH (0.5 N, 5 ml) was stirred for 24 h, after which the saponification was quantitative. Following acidification with 10% HCl (pH = 2), the mixture was cooled with ice and extracted with $Et_2O$ (4 × 25 ml). The combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated under reduced pressure. The acid was used without further purification. A solution of the acid and $Ag_2CO_3$ (50 mg, 2.0 mmol) in toluene (5 ml) was refluxed under argon for 16 h. The mixture was then filtered through Celite, the adsorbent washed with toluene, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 95:5) to give 0.13 g (73% from **13**) of **1c**. – $R_f$ = 0.15 (petroleum ether/ethyl acetate, 95:5). – IR (film): $\tilde{\nu}$ = 2943 $cm^{-1}$, 2868, 1799, 1651. – $^1H$ NMR ($CDCl_3$): δ = 1.26–1.32 (m, 1H), 1.34 (s, 3H, $CH_3$), 1.42–2.29 (m, 7H), 1.88 (s, 3H, $CH_3$), 4.53 (d, *J* = 2.3 Hz, 1H, $=CH_2$), 4.97 (d, *J* = 2.3 Hz, 1H, $=CH_2$). – $^{13}C$ NMR ($CDCl_3$): δ = 17.9 (t), 19.8 (q), 24.1 (q), 27.8 (t), 31.7 (t), 42.9 (s), 91.1 (t, $=CH_2$), 127.9 (s, =C), 135.0 (s, =C), 153.8 (s, =C), 178.6 (s, CO). – GC-MS (80 eV); *m/z* (%): 179 (12) [M + 1], 166 (48), 149 (15), 135 (30), 119 (75), 109 (67), 91 (100), 79 (48). – $C_{11}H_{14}O_2$ (178.2): calcd. C 74.13, H 7.92; found C 73.94, H 8.17.

*3a,9b-Dimethyl-8-phenyl-1,2,3,3a,6,9b-hexahydro-5-oxa-6a,8,9a-triazacyclopenta[e]acenaphthylene-4,7,9-trione* (**16**): Diene **1a** was dissolved in $CH_2Cl_2$, cooled to −78°C, and then *N*-phenyl-1,2,4-triazolidinone (0.05 g, 0.26 mmol) was added. After 10 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The solvent was evaporated under reduced pressure and the remaining oily residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 1:1), affording **16** as a colourless solid (45 mg, 45%). – M. p. 216°C. – $R_f$ = 0.41 (petroleum ether/ethyl acetate, 1:1). – IR (KBr): $\tilde{\nu}$ = 2952 $cm^{-1}$, 2368, 1805, 1762, 1691. – $^1H$ NMR ($CDCl_3$): δ = 1.53 (s, 3H, $CH_3$), 1.56 (s, 3H, $CH_3$), 1.63–2.18 (m, 4H, 2-H, 3-H), 3.86–3.93 (m, 1H, 1-H), 4.19 (d, $^2J$ = 16.0 Hz, 1H, 6-H), 4.75 (d, $^2J$ = 16.0 Hz, 1H, 6-H), 5.83 (s, OH), 7.43–7.55 (m, 5H). – $^{13}C$ NMR ($CDCl_3$): δ = 15.6 (q), 22.1 (q), 27.1 (t), 31.3 (t), 43.1 (t, C-6), 45.2 (s, C-3a), 66.5 (s, C-9b), 76.1 (d, C-1), 119.8 (s), 125.9 (d), 129.4(d), 129.8 (d), 130.7 (s), 142.2 (s), 153.2

(s, CO), 153.8 (s, CO), 179.8 (s, CO). – GC-MS (80 eV); *m/z* (%): 369 [$M^+$] (89), 326 (32), 250 (25), 193 (91), 190 (91), 178 (30), 151 (66), 150 (31), 123 (42), 122 (36), 120 (50), 119 (96), 95 (30), 91 (91), 77 (88), 53 (47). – $C_{19}H_{19}N_3O_4$ (353.4): calcd. C 61.78, H 5.18, N 11.38; found C 61.96, H5.13, N 11.06.


[1] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis (Tetrahedron Organic Chemistry Series*, vol. 8), Pergamon Press, Oxford, **1990**. J. Sauer, R. Sustmann, *Angew. Chem.* **1980**, *92*, 773–801; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779.

[2] G. Desimoni, G. Tacconi, A. Barco, G. P. Pollini, *Natural Products Synthesis through Pericyclic Reactions, ACS Monogr.* **1986**, *180*, chapter 5. E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*, J. Wiley & Sons, New York, **1989**. K. C. Nicolaou, E. J. Sorenson, *Classics in Total Synthesis*, VCH, Weinheim, **1996**.

[3] K. Maruoka, H. Yamamoto in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, Weinheim, **1993**, chapter 9. H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007–1019. J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn, H. U. Reissig, *Organic Synthetic Highlights*, VCH, Weinheim, **1991**, 61–63, 66–70. E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617.

[4] J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn, H. U. Reißig, *Organic Synthetic Highlights*, VCH, Weinheim. **1991**, 60–61. K. Krohn, *Angew. Chem.* **1993**, *105*, 1651–1653; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1582–1584.

[5] G. Helmchen, R. Karge, J. Weetman in *Modern Synthetic Methods*, vol. 4 (Ed.: R. Scheffold), Springer, Berlin, **1986**, 261–306. J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn, H. U. Reissig, *Organic Synthetic Highlights*, VCH, Weinheim, **1991**, 54–60.

[6] D. Enders, O. Meyer, G. Raabe, *Synthesis* **1992**, 1242–1244. J. Barluenga, F. Aznar, C. Valdes, A. Martin, S. Garcia-Granda, E. Martin, *J. Am. Chem. Soc.* **1993**, *115*, 4403–4404.

[7] R. M. Guiliano in *Cycloaddition Reactions in Carbohydrate Chemistry* (Ed.: R. M. Guiliano), *ACS Symp. Ser.* **1992**, *494*, 1–23. R. W. Franck, *ibid.*, 24–32. J. Christobal Lopez, G. Lukacs, *ibid.*, 33–49.

[8] M. J. Fisher, W. J. Hehre, S. D. Kahn, L. E. Overman, *J. Am. Chem. Soc.* **1988**, *110*, 4625–4633. S. C. Datta, R. W. Franck, R. Tripathy, G. J. Quigley, L. Huang, S. Chen, A. Sihaed, *J. Am. Chem. Soc.* **1990**, *112*, 8472–8478. I. Fleming, A. K. Sarkar, M. J. Doyle, P. R. Raithby, *J. Chem. Soc., Perkin Trans. 1* **1989**, 2023–2030. W. Adam, J. Gläser, K. Peters, M. Prein, *J. Am. Chem. Soc.* **1995**, *117*, 9190–9193.

[9] Y. Hayashi, T. Matsumoto, T. Sakan, *Heterocycles* **1978**, *10*, 123. For synthesis of nagilactones see: Y. Hayashi, T. Matsumoto, M. Nishizawa, M. Togami, T. Hyono, N. Nishikawa, M. Uemura, *J. Org. Chem.* **1982**, *47*, 3428–3433. S. D. Burke, M. E. Kort, S. M. S. Strickland, G. M. Organ, L. A. Silks, *Tetrahedron Lett.* **1994**, *35*, 1503–1506.

[10] B. Westermann, I. Kortmann, *Tetrahedron: Asymmetry* **1993**, *4*, 2119–2122. B. Westermann, I. Kortmann, *Biocatalysis* **1994**, *10*, 289–294.

[11] Lipodex E is available from Macherey & Nagel, Düren, Germany.

[12] J. d'Angelo, D. Desmaele, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459–505. K. H. Ellermann, Dissertation, University of Paderborn, Germany, **1990**.

[13] T. Kitahara, K. Touhara, H. Watanabe, K. Mori, *Tetrahedron* **1989**, *45*, 6387–6400. P. Q. Huang, W. S. Zhou, *Tetrahedron: Asymmetry* **1991**, *2*, 875–878.

[14] An allylic rearrangement of a molecule showing a similar substituent pattern has been observed by Mori[13] as a side reaction.

[15] P. Pale, J. Chuche, *Tetrahedron Lett.* **1987**, *28*, 6447–6450.

[16] D. Liotta, D. Brown, W. Hoekstra, R. Monahan III, *Tetrahedron Lett.* **1987**, *28*, 1069–1072.

[17] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

[18] NOEs have been observed in similar molecules: R. Hoffmann, J. Mattay, *Liebigs. Ann.* **1995**, 1455–1461.


[96136]