Regio- and Stereoselective Diels–Alder Additions of Maleic Anhydride to Conjugated Triene Fatty Acid Methyl Esters


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The thermal, solvent-free addition of maleic anhydride to methyl calendulate (methyl 8,10-trans,12-cis-octadecatrienoate) (1a) occurs with very high regio- and stereoselectivity at C-8 and C-11 of the fatty compound giving the endo-Diels–Alder adduct 4 with retention of the cis-configured double bond. Analogously, the Diels–Alder addition of maleic anhydride to methyl α-eleostearate (methyl 9-cis,11,13-trans-octadecatrienoate) (2a) takes place regio- and stereoselectively at C-11 and C-14 yielding the endo-product 5 which was hydrolyzed to give the respective tricarboxylic acid 6. X-ray diffraction analyses of compounds 4 and 6 clearly show the regio- and stereoselectivity of the Diels–Alder addition reactions.

Introduction

Regio- and stereoselective reactions are of great interest in organic synthesis. In recent years, our interest has been focused on carbon–carbon bond-forming addition reactions to unsaturated fatty compounds such as oleic acid and 10-undecenoic acid, to obtain new branched and/or chain elongated highly functionalized fatty compounds with possibly interesting properties. However, most of the electrophilic addition reactions as, for example, Friedel–Crafts acylations, Friedel–Crafts alkylation and ene additions to mono-unsaturated fatty compounds such as oleic acid gave 1:1 mixtures of two regioisomeric addition products, which could not be separated.[1,2] Solvent-free thermal reaction at 190 °C of maleic anhydride and mono-unsaturated fatty acid methyl esters such as methyl oleate gave the respective ene-addition products as regioisomeric and diastereomeric mixtures.[3]

Recently, we described highly regioselective carbon–carbon bond-forming additions to the reactive enyne system of methyl santalbate [methyl (E)-octadec-11-en-9-ynoate][4] and highly regio- and diastereoselective Prins-type cyclizations of methyl ricinoleate [methyl (9Z,12R)-12-hydroxy-9-octadecenoate] with aldehydes.[5]

Calendic acid (8,10-trans,12-cis-octadecatrienoic acid) (1) is the main fatty acid with a content of up to 59% in the seed oil of Calendula officinalis L. (Compositae).[6] α-Eleostearic acid (9-cis,11,13-trans-octadecatrienoic acid) (2) is the most commonly occurring conjugated triene acid which is found e.g. in the oil of the nuts of the tung oil tree.[7] Tung oil is used as a drying oil for a number of products including varnishes, resins, inks, paints and coatings. Because of its excellent properties there are attempts to increase the production of tung oil in the United States and to introduce new uses of the oil in consumer products.[8] Punicic acid (9,13-cis,11-trans-octadecatrienoic acid) (3) is the main fatty acid of the seed oil of pomegranate[7] (Figure 1).

Figure 1. Calendic acid (8,10-trans,12-cis-octadecatrienoic acid) (1), α-eleostearic acid (9-cis,11,13-trans-octadecatrienoic acid) (2) and punicic acid (9,13-cis,11-trans-octadecatrienoic acid) (3). In the experiments described in this article the respective methyl esters 1a, 2a and 3a were used.

Highly regioselective Diels–Alder addition products of maleic anhydride and conjugated triene fatty acids such as calendic acid (1) and α-eleostearic acid (2) were described in literature.
The reaction of calendic acid (1) and maleic anhydride which was performed in benzene yielded the Diels–Alder addition product regioselectively to the trans double bonds in positions C-8 and C-11 of the fatty acid with retention of the cis double bond at C-12.\cite{9,10} Interestingly, the reaction was carried out to assign the configuration of 1 by analysis of the degradation products of the Diels–Alder addition product. It is remarkable that only one single addition product was obtained. Paschke et al., also using the Diels–Alder addition of maleic anhydride for determination of the configuration of eleostearic acids, observed a higher reactivity of the all-trans-β-eleostearic acid compared to α-eleostearic acid in this reaction.\cite{11} However, the stereochemistry of the Diels–Alder addition products was not discussed.

In this paper, we report on the thermal solvent-free addition of maleic anhydride to the highly reactive conjugated triene systems of methyl calendulate (1a) and methyl α-eleostearate (2a) and X-ray structure analysis of the Diels–Alder addition products.

Results and Discussion

We obtained methyl calendulate (1a), methyl α-eleostearate (2a) and methyl punicate (3a) by transesterification of calendula oil, tung oil, and pomegranate oil, respectively, with methanol in the presence of sodium methylate. No isomerization of the 8,10-trans,12-cis-1a, 9-cis,11,13-trans-2a, and 9,13-cis,11-trans-3a double bonds, respectively, was observed.

The addition of maleic anhydride to methyl calendulate (1a) without any solvent at 150 °C under nitrogen yielded the Diels–Alder adduct 4 after a reaction time of 2 h in an isolated yield of 78% (Scheme 1).

![Scheme 1. Regio- and stereoselective thermal Diels–Alder reaction of methyl calendulate (1a) and maleic anhydride.](image)

Compound 4 was separated from the reaction mixture by column chromatography and recrystallized from petroleum ether/diethyl ether (4:1). Ene adducts which could be thought to be formed by reaction of the by-products of 1a i.e. linoleic acid and oleic acid with maleic anhydride were not observed. Obviously the ene reaction is considerably slower than the Diels–Alder reaction at the used reaction temperature. The pure product 4 (m.p. 42–43 °C) was identified by $^1$H and $^{13}$C NMR spectroscopy as well as mass spectrometry. In analogy to the results of Chisholm and Hopkins\cite{9,10} the solvent-free reaction, too, took place regioselectively at C-8 and C-11 with retention of the (Z)-configured $\Delta^{12,13}$ bond which was confirmed by analysis of the vicinal coupling constants $J_{12,13} = 10.7$ Hz. Diels–Alder reactions of polyenes are well known showing a well-defined preference for (E)-configured substrates. Thus, trans-1,3,5-hexatrienes were found to combine with maleic anhydride much faster than the respective cis isomers.\cite{12}

Furthermore, the X-ray diffraction analysis of compound 4 unambiguously reveals the regio- and stereoselectivity of the Diels–Alder addition to C-8 and C-11 giving the endo addition product with retention of the (Z)-configured double bond at C-12 (Figure 2). Our results concerning the regioselective 1,4-cycloaddition of the dienophile to the trans,trans double bonds of 1a giving the all-cis tetra-substituted cyclohexene derivative 4 as well as the endo stereochemistry of 4 are consistent with the general requirements of the Diels–Alder reaction.\cite{13} The formation of regio- and stereoisomeric products should only be possible as a consequence of isomerization of the double bonds which could not be observed. Compound 4 should be of interest for the synthesis of polyesters and polyamides.

The thermal addition of maleic anhydride to methyl α-eleostearate (2a) was carried out in analogy to the respective reaction of methyl calendulate (1a) yielding the expected Diels–Alder adduct 5 (Scheme 2). In this reaction, too, the addition took place regioselectively to the (E)-configured double bonds in positions C-11 and C-14 of 2a with retention of the (Z) double bond at C-9. Already after a reaction time of 30 min. 2a was quantitatively reacted to the Diels–Alder adduct 5 which was isolated in 62% yield. Unfortunately, for compound 5 it was not possible to obtain crystals of sufficient quality for an X-ray structure analysis. Thus, 5 was hydrolyzed with diluted sulfuric acid. The ring-opened product 6 with a tricarboxylic acid functionality was obtained in approximately quantitative yield.

Compound 6 was crystallized from petroleum ether/diethyl ether (4:1). The X-ray diffraction analysis clearly
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Scheme 2. Regio- and stereoselective thermal Diels–Alder reaction of methyl α-eleostearate (2a) and maleic anhydride yielding the Diels–Alder product 5 followed by ring-opening with sulfuric acid to give the tricarboxylic acid 6.

shows the regio- and endo-stereoselectivity of the Diels–Alder addition to C-11 and C-14 (Figure 3). As shown in Figure 4 the molecules of compound 5 are associated in the solid by hydrogen bonds.

Furthermore, we performed the thermal solvent-free addition of maleic anhydride to the conjugated triene system of punicic acid methyl ester (3a) which was obtained from the seed oil of Punica granatum. As expected Diels–Alder addition occurred, however, the product consists of a mixture of at least five regio- and stereoisomeric products as a consequence of the alternating cis/trans double bonds in the substrate. No separation and isolation of the isomers was performed.

Conclusions

Thermal solvent-free Diels–Alder reactions of maleic anhydride with the conjugated triene systems of methyl calendulate and methyl α-eleostearate occur with high yields regioselectively and stereoselectively at the conjugated (E)-configured double bonds with retention of the (Z) double bond. X-ray structure analysis of the products 4 and 6 showed the all-cis configured tetra substituted endo-cyclohexene derivatives.

Experimental Section

General: Calendula oil (57% calendic acid, 26% linoleic acid, 3% oleic acid, 2% palmitic acid) and pomegranate oil (84% punicic acid, 4% linoleic acid, 3% oleic acid, 2% palmitic acid) were obtained by hexane extraction of the seeds of Calendula officinalis and Punica granatum, respectively, and tung oil (78% α-eleostearic acid, 6% oleic acid, 4% linoleic acid, 2% palmitic acid) was purchased from biopin GmbH, Jever, Germany. The amounts of the fatty acids were determined by transesterification of the oils with methanol and GC of the respective methyl esters. The amounts of the starting olefins, methyl calendulate (57% purity, 1a), methyl α-eleostearate (78% purity, 2a) and methyl punicate (84% purity, 3a), used in the reactions, were calculated based on 100% purity. For column chromatography Merck 60 silica gel, 70–230 mesh, was used.

Analytical Equipment: Analytical GC was performed with a Carlo–Erba GC series 4160 with an FID detector and fused silica capillary column DB1, 29 m. 1H and 13C NMR spectra were recorded in CDCl3 with a Bruker DRX 500 spectrometer at 300 K using residual non-deuterated solvent (1H NMR) or CDCl3 (13C NMR) as internal standards. Mass spectra were recorded with a Finnigan MAT 95. All products were unambiguously identified by 1H and 13C NMR and by MS (EI) or GC/MS (EI). Single-crystal X-ray structure studies were carried out with a Stoe IPDS single crystal diffractometer.

Methyl rel-7-\{(3aS,4S,7R,7aR)-4-[(Z)-Hept-1-enyl]-1,3,3a,4,7,7a-hexahydro-1,3-dioxoisobenzofuran-7-yl]heptanoate (4): A mixture of calendic acid methyl ester (1a) (5 mmol, 1.50 g) and maleic anhydride (5 mmol, 0.49 g) was heated for 2 h at 150 °C under nitrogen. The reaction was followed by thin-layer chromatography [petroleum ether/diethyl ether (7:3), Rf(1a) = 0.60, Rf(4) = 0.23]. Purification of product 4 was achieved by column chromatography [silica
gel using petroleum ether/diethyl ether (7:3) and petroleum ether/ethyl acetate (1:1) as eluent). Fractions containing product 4 were collected and the solvent was removed in vacuo. Compound 4 was recrystallized from petroleum ether/diethyl ether (4:1) for X-ray diffraction analysis. M.p. 42–43 °C. Yield 0.87 g (75%). 1H NMR (300.1 MHz, CDCl3): δ = 5.85 (m, 3 H), 5.65 (dt, J = 10.6, 7.5 Hz, 1 H), 3.67 (s, 3 H), 3.39 (m, 2 H), 3.25 (m, 1 H), 2.32 (t, J = 7.5 Hz, 2 H), 2.08 (dt, J = 7.1, 7.3 Hz, 2 H), 1.95–1.70 (m, 2 H), 1.65 (tt, J = 7.3, 7.0 Hz, 2 H), 1.54–1.24 (m, 12 H), 0.90 (t, J = 6.4, 1.7 Hz, 3 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 174.4, 171.3, 171.2, 133.5, 133.4, 132.9, 126.9, 51.3, 46.3, 44.4, 36.1, 33.9, 33.5, 31.3, 30.5, 29.0, 29.0, 28.8, 27.6, 27.2, 24.7, 22.4, 13.9 ppm. GC/MS (EI): m/z (%): 390 (2), 359 (17), 318 (33), 291 (27), 189 (37), 91 (100). HR-MS/ESI C23H22O5 calcld. 390.2406; found 390.2405.

Crystal Structure Analyses: C23H22O5; triclinic; P1; colorless needle; a = 5.4679(10) Å, b = 9.0567(2) Å, c = 22.103(6) Å, α = 96.823(3)°, β = 90.353(3)°, γ = 95.773(3)°; V = 1081.14(4) Å³; Z = 2; T = 193(2) K; λ = 0.71073 Å; 13678 reflections, 3894 independent; R1 = 0.0352 [I > 2σ(I)], wR2 = 0.0915 (for all data); μ = 0.083 mm⁻¹; full-matrix, least-squares on F².[14]

Methyl rel-(9Z)-10-[(3a,4S,7R,7aR)-4-Butyl-1,3,3a,4,7,7a-hexahydro-1,3-dioxoisobenzofuran-7-yl]dec-9-enoate (5): A mixture of α-oleostearic acid methyl ester (2a) (11.7 mmol, 4.50 g) and maleic anhydride (15 mmol, 1.47 g) was heated for 30 min at 150 °C under nitrogen. The further work-up was carried out as described above for product 4. Yield 2.83 g (62%). 1H NMR (300.1 MHz, CDCl3): δ = 5.85 (m, 3 H), 5.65 (dt, J = 10.6, 7.5 Hz, 1 H), 3.67 (s, 3 H), 3.39 (m, 2 H), 3.25 (m, 1 H), 2.32 (t, J = 7.5 Hz, 2 H), 2.08 (dt, J = 7.1, 7.3 Hz, 2 H), 1.95–1.70 (m, 2 H), 1.65 (tt, J = 7.3, 7.0 Hz, 2 H), 1.54–1.24 (m, 12 H), 0.90 (t, J = 6.4, 1.7 Hz, 3 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 174.1, 171.3, 171.2, 133.6, 133.5, 132.8, 127.1, 51.3, 46.4, 44.5, 36.2, 33.9, 33.6, 30.3, 30.1, 29.3, 29.0, 27.3, 24.8, 22.5, 13.9 ppm. MS (EI): m/z (%): 390 (12), 359 (31), 344 (38), 318 (31), 291 (46), 287 (58), 147 (80), 91 (100). HR-MS/ESI C23H22O5 calcld. 390.2406; found 390.2407.

all-cis-3-Butyl-6-(Z)-9-carboxynon-1-enylcyclohex-4-ene-1,2-dicarboxylic Acid (6): A mixture of product 5 (1.3 mmol, 0.5 g) and H2SO4 (3 mL) and concd. H2SO4 (1 drop) was heated under reflux for 24 h. After the mixture had cooled to room temperature diethyl ether (30 mL) was added and the organic layer was washed several times with water. The organic layer was separated and dried with anhydrous sodium sulfate. After filtration the solvent was removed in vacuo. Yield 0.44 g (88%). The residue was resolved in diethyl ether and compound 6 was recrystallized for X-ray diffraction analysis from diethyl ether/petroleum ether. M.p. 98–100 °C. 1H NMR (500.1 MHz, CDCl3): δ = 5.61 (2×dd, J = 10.4, 9.9 Hz, 2 H), 5.55 (dd, J = 10.4, 6.0, 2.7 Hz, 1 H), 5.41 (dt, J = 10.4, 7.1, 1 H), 3.19 (dd, J = 7.1, 3.8 Hz, 1 H), 3.10 (dd, J = 4.9, 4.9 Hz, 1 H), 2.32 (m, 3 H), 2.11 (m, 1 H), 2.03 (m, 1 H), 1.63(m, 2 H), 1.54 (m, 1 H), 1.46 (m, 1 H), 1.31 (m, 12 H), 0.88 (t, J = 7.1 Hz, 3 H) ppm. 13C NMR (125.8 MHz, CDCl3): δ = 180.6, 180.0, 177.7, 132.4, 128.6, 128.2, 127.7, 46.0, 42.2, 37.5, 34.6, 34.0, 32.0, 29.7, 29.3, 28.9, 28.8, 28.7, 27.0, 24.6, 22.6, 14.0 ppm. MS/CI (isobutane): m/z (%): 437 (100) [M⁺ – HCl], 405 (32). HR-MS/ESI C23H22O5 calcld. 394.2355; found 394.2354.

Crystal Structure Analyses: C23H22O5; triclinic; P1; colorless plate; a = 9.0365(7) Å, b = 11.5103(9) Å, c = 11.9705(12) Å, α = 71.489(10)°, β = 88.620(11)°, γ = 69.093(9)°; V = 1097.33(19) Å³; Z = 2; T = 193(2) K; λ = 0.71073 Å; 13607 reflections, 4038 independent; R1 = 0.0419 [I > 2σ(I)], wR2 = 0.0869 (for all data); μ = 0.086 mm⁻¹; full-matrix, least-squares on F².[14]