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High-pressure and thermally induced intramolecular Diels–Alder reactions of furfuryl fumarates. Influence of tether substituents on diastereoselectivity

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Abstract: Asymmetric intramolecular Diels–Alder (IMDA) reactions of optically active furfuryl fumarates result after crystallization in enantiopure 7-oxabicyclo[2.2.1]heptene derivatives that may be useful building blocks for natural product synthesis. The influence of high-pressure and thermal activation has been studied for these cycloadditions. The diastereoselectivities observed increase with the size of the tether substituents, but not linearly. A possible explanation based on transannular interactions is given. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Enantiopure 7-oxabicyclo[2.2.1]heptene derivatives have been shown to be valuable key intermediates for the synthesis of important types of natural products.[1] A large number of selective transformations of the 7-oxabicyclo[2.2.1]heptene system endow this nucleus with impressive versatility.[2] The C=C double bond for example may easily be functionalized by epoxidation or (asymmetric) dihydroxylation with the bicyclic ring system helpfully giving advantage to an *exo*-selective reagent attack. Regioselective hydrogenation or oxidative cleavage may also take place. Alternatively one of the C–O bonds may be cleaved by treatment with a strong nucleophile. This results in a ring opening of the oxabicyclic system yielding a wide variety of cyclohexane chirons.[3]

Asymmetric synthesis of these building blocks has been achieved mostly by the intermolecular cycloaddition of furan with chiral acrylates[4] or with acrylates in the presence of chiral catalysts.[5] However, the asymmetric *intramolecular* Diels–Alder (IMDA) reaction with furan as the diene moiety has received less attention, despite its intramolecular advantages like entropy acceleration[6] and conformational diastereoselection,[7] which may extend the scope and usefulness of the DA route. The first example for the intramolecular approach was reported by Mukaiyama[8] illustrating the use of a removable chiral auxiliary. Recently, two similar systems based on *N*-substituted furfuryl amines have been described.[9]

In this paper, we describe the highly stereoselective synthesis and cyclization of optically active furfuryl fumarates as part of a major study in our laboratory. The influence of both thermal and high-pressure activation has been investigated. The results will be compared and discussed with respect to the concepts of conformational restrictions as a consequence of the anchor qualities of the tether substituent[10] and of allylic 1,3-strain (^{1,3}A-strain).[11]

Results and discussion

The preparation of the DA precursors **3a–f** is illustrated in Scheme 1. Furfural **1** was converted to the racemic alcohol **2** in a typical Grignard procedure. For R=*t*Bu the corresponding lithium alkyl was used for purposes of higher reactivity. The partial oxidation of **2** with Sharpless reagents[12,13] left the (*R*)-configured alcohols (+)-**2** with high enantiomeric excesses (93–99% e.e., Table 1), except for alcohol

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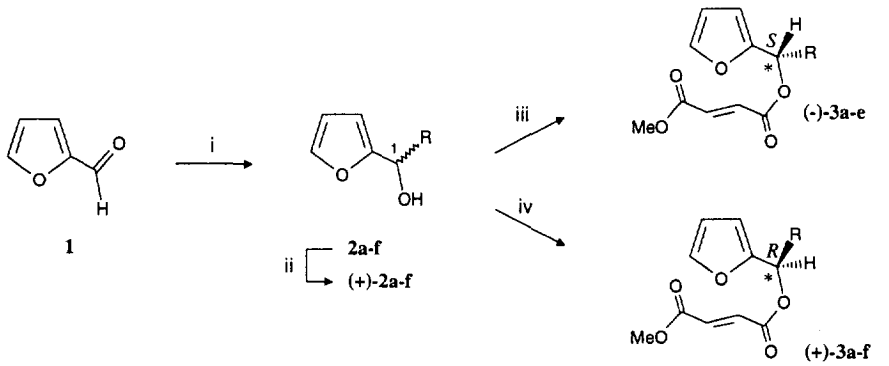
2d (R=*t*Bu). The IMDA precursors **3** were established by coupling the enantiomerically enriched diene units with fumaric acid mono methyl ester, either under Mitsunobu conditions with concomitant inversion of stereochemistry yielding (−)-**3** or with retention upon sequential treatment with *n*BuLi and fumaroyl chloride mono methyl ester giving (+)-**3** (cf. Scheme 1, yields: 41% (R=*neo*Pn) to 81% (R=Me)). Both ways are complementary to each other with respect to the chirality of the stereogenic center at C-1 and therefore add to the flexibility of the overall synthetic scheme.



Scheme 1. Reagents: i. RMgBr, for **2d**: *t*BuLi; ii. 0.6 eq *t*BuOOH, Ti(O*i*Pr)$_4$, *L*-(+)-DIPT, 4 Å ms; iii. DEAD, PPh_3, $MeO_2CCH{=}CHCO_2H$; iv. (a) BuLi, THF, (b) 0.5 eq DMAP, toluene, 2.0 eq $MeO_2CCH{=}CHCOCl$.

The furfuryl fumarates **3** were completely cyclized in dry acetone at 40°C under high-pressure conditions (up to 7.5 kbar) within 18 h. As illustrated in Scheme 2 two diastereomeric adducts (**6*R*)-4** and (**6*S*)-5** are formed. After ^{1}H-NMR analysis the evaporated crude product was purified by flash column chromatography (FC) and the major adducts could be isolated in 1–2 recrystallization steps from methanol, except for adducts **4a/5a**, which could be resolved neither by flash chromatography nor by crystallization. Alternatively, the cycloaddition may be activated thermally. For reasons of comparison we fixed the temperature again at 40°C, but in this case equilibrium was reached only after 5–7 days and starting material remained. Further investigation was therefore curtailed.

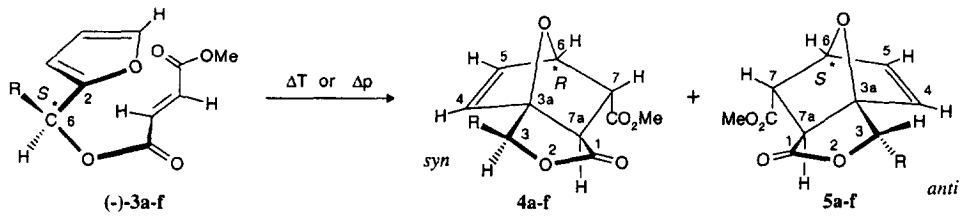
The diastereoselectivity does not change using high pressure, except for the adduct pair **4c/5c** substituted with the anisotropic *i*Pr-group (cf. Scheme 2). In contrast to other studies[14] which deal exclusively with *exo*/*endo*-stereoisomers here we have two *exo*-adducts with very similar structures and activation volumes. Computer calculations[15] for example indicate only a $\Delta\Delta V^{\ddagger}$ of 0.2–0.4 cm^3/mol.

There is evidence that cycloadducts **4** and **5** are in equilibrium via a *retro*-DA–DA-sequence.[16] This has also been found by Jung and Gervay investigating similar systems.[17] Thus, the diastereoselectivity observed should be thermodynamically controlled. But when we heated a pure sample of the major

Table 1. Kinetic resolution of racemic alcohols **2**. Conditions: catalytic amounts of Ti(O*i*Pr)$_4$/*L*-(+)-DIPT and 4 Å molecular sieves (method A) or stoichiometric amounts of Ti(O*i*Pr)$_4$/*L*-(+)-DIPT (method B)

alcohol	R	method	reaction time	temp.	% yield of **2**	% e.e.*
2a	Me	A	12 h	-21 °C	25	98
2b	Et	A	13 h	-21 °C	43	99
2c	*i*Pr	B	25 h	-21 °C	35	99
2d	*t*Bu	B	40 h	-21 °C	36	8
2e	*neo*Pn	B	24 h	-21 °C	28	93
2f	Ph	A	48 h	-21 °C	14	>95†

*Chiral phase GC analysis (MACHERY & NAGEL Lipodex-C, 50 m). †Determined by ^{1}H-NMR spectroscopy (400 MHz) of the MTPA ester of (+)-**2f**.



diester	R	cyclization	% yield of **4** + **5**	ratio of **4** : **5***	% d.e.
(-)-**3a**	Me	high-pressure	96	55 : 45	10
		thermal	41	55 : 45	10
(-)-**3b**	Et	high-pressure	36	68 : 32	36
(-)-**3c**	*i*Pr	high-pressure	90	90 : 10	80
		thermal	31	78 : 22	56
(-)-**3d**	*t*Bu	high-pressure	92	93 : 7	86
		thermal	44	92 : 8	84
(-)-**3e**	*neo*Pn	high-pressure	93	69 : 31	38
(+)-**3f**	Ph	high-pressure	49†	23 : 77†	54

Scheme 2. Thermal reaction: acetone, 40°C, 5–7 days; high-pressure reaction: acetone, 40°C/7 kbar, 18 h. Note: for R=Ph the *R*-configured precursor (+)-**3f** was utilized. (*Evaporated crude product; determined by ^{1}H-NMR spectroscopy (400 MHz). †*epi*-**4** and *epi*-**5** with respect of stereocenter at C-3 (cf. note 27)).

adduct **4d** in dry chloroform for 4 hours at 60°C we only isolated **4d** back again with some polymeric by-products.[18]

According to literature results,[19] only the diastereomeric adducts **4** and **5** which are *trans*-fused have been formed. Additionally, the adduct **4** (or *epi*-**5** for **3f**!) with the tether substituent R oriented *syn* with respect to the oxygen bridge predominates up to a 9:1 ratio depending on the size of tether substituent R. This demonstrates a remarkable chirality transfer from the stereocentre on the sidearm to the resulting oxabicyclo[2.2.1]heptene nucleus. Four new stereocentres of known absolute stereochemistry have been generated by utilizing transannular interactions in only one step.

The relative stereochemistry of all adducts has been investigated by NOE difference spectroscopy. To our surprise the major isomers exhibited two strong enhancements at 4-H and 8-H on irradiation at 3-H (Figure 1a). For the minor isomer we found one rather strong enhancement between 3-H and 4-H, but one weak enhancement between 3-H and 8-H! The structure therefore has been finally proven by X-ray analysis[20] of diastereomer **4d** (Figure 1b, R=*t*Bu).

The position of substituent R results from balancing the nonbonding interactions with the oxygen bridge on the one hand and the olefinic atom 8-H on the other hand. Obviously the equatorial position is less favorable. One might argue that the product distribution observed results from thermodynamic control and the *syn*-position of substituent R is conformationally preferred. But the diastereoselectivities correlate only roughly with the anchor qualities of R. This has been checked using the A values of Hirsch.[10a] We think the *syn*-preference of the reaction is also in line with the assumption that in the transition state (TS) the tether conformation is controlled by ^{1,3}A-strain between 4-H (cycloadduct's notation) and substituent R. Consequently the dienophile attack is only possible with the substituent R is not coplanar with the furan ring.

This explanation has been confirmed, when we substituted 4-H by a methyl group. The synthetic route to the corresponding cycloadduct **11** with R=Me is given in Scheme 3. Starting with 4,4-dimethoxy-2-butanone and methyl chloroacetate 2-methyl-furfural **8** was synthesized in 3 steps with an overall yield of 16%. One unsolved problem is the tremendous instability of alcohol **7**. Compound

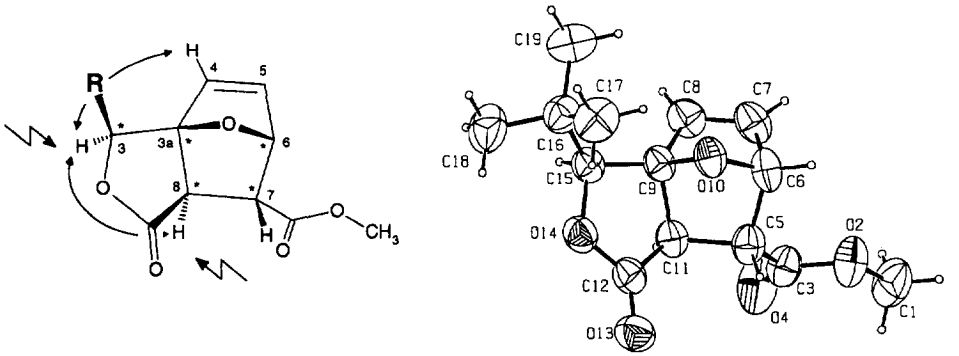
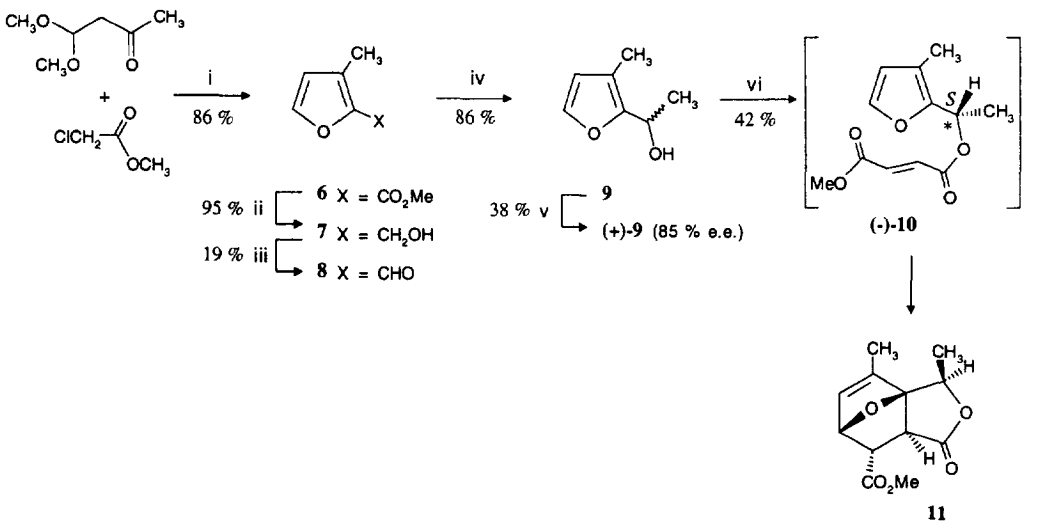


Figure 1. Structure elucidation of the major isomer **4**: (a) NOE contacts on irradiation at H3 and H8; (b) *ORTEP* drawing of **4d** (R=*t*Bu) with crystallographic numbering system. Ellipsoids are drawn at the 50% probability level while isotropic H-atom thermal parameters are represented by spheres of arbitrary size.

8 acts as a versatile intermediate for the introduction of several tether substituents. Conversion to enantiomerically enriched alcohols, e.g. **(+)-9**, was achieved in an analogous manner to Scheme 3. The mediocre enantioselectivity of the Sharpless kinetic resolution in this case may be increased by optimizing the reaction conditions (cf. Experimental section). Alcohol **(+)-9** was then converted to the diester **(−)-10**. To our surprise the extra methyl group of the furan moiety dramatically effects the cycloaddition course. Not only was the reaction speeded up but no IMDA precursor **(−)-10** could be isolated, π-facial selectivity being increased to ca. 100% d.e. in favor of the *syn* adduct **11**. Clearly the strong ^{1,3}A-strain between the two methyl groups destabilizes the concurrent TS, so that **11** is the sole product.



Scheme 3. Reagents: i. (a) NaOMe, −10 to −5°C, (b) 160°C; ii. 0.5 eq $LiAlH_4$, THF, 25°C; iii. MnO_2, CH_2Cl_2, 25°C; iv. MeMgJ; v. 0.6 eq *t*BuOOH, $Ti(OiPr)_4$, *L*-(+)-DIPT, 4 Å ms; vi. DEAD, PPh_3, $MeO_2CCH{=}CHCO_2H$.

Of course, if the synthetic objective does not require the presence of a methyl substituent in the olefinic position, the temporary introduction of a dummy substituent, e.g. R=–Br or –$SiMe_3$, will probably result in equally high levels of asymmetric induction. This may open one very general synthetic route to polyfunctional, enantiopure 7-oxabicyclo[2.2.1]heptene derivatives. Further

investigations with this goal in mind and exploitation of the synthetic potential of the products obtained, e.g. selective epoxy-ring opening and dihydroxylation of the C=C double bond, are planned.

Experimental

General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Standard drying methods[21] were used. Unless otherwise stated, yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous materials. None of the procedures were optimized. TLC: for reaction monitoring, *Merck* silica gel 60 F_{254}, detection by quenching of the fluorescence and/or by charring with gaseous iodine. Flash column chromatography (FC): *Merck* silica gel 60 (particle size 0.040–0.063 mm). M.p. (uncorrected): *Tottoli* apparatus *Büchi SMP 20*. Optical rotations: *Perkin Elmer 241 MC* at 589 nm and 25°C. IR spectra: *Beckmann Akkulab 1*, ν_{max} in cm^{-1}, only the characteristic peaks are given. ^{1}H-NMR spectra (δ [ppm] from TMS, apparent coupling constants J [Hz]): 250 MHz: *Bruker AC 250*. 400 MHz: *Bruker ARX 400*. ^{13}C-NMR spectra (δ [ppm] from TMS, multiplicities as determined from DEPT spectra): 100 MHz: *Bruker ARX 400*. NOE spectra: 400 MHz: *Bruker ARX 400*, irradiated signal → affected signal(s). Signals of low intensity are put in parentheses. GC: *HP-5890 Series II*, H_2 pressure 1.3 bar, constant temperature program (60 or 70°C), column: *Machery & Nagel Lipodex® C* (50 m). Elemental analyses were carried out by the *Mikrolabor Universität Regensburg*.

Furfuryl alcohols **2** were prepared according to reported procedures.[22] Their kinetic resolution was achieved as described in the literature.[12,13] Both the catalytic method A with catalytic amounts of Ti(O*i*Pr)$_4$ and *L*-(+)-DIPT (**2a–b, 2f**) and the stoichiometric method B (**2c,d**) were utilized. The scope of the reaction was extended to alcohols **2e** and **9** in a similar way. The optical purity of **2** was confirmed by chiral phase GC (Lipodex-C column, 50 m). Their physical data are described below or in the literature.[12] Methyl 3-methyl-2-furoate **6** was prepared according to an organic synthesis protocol.[23]

(1R)-2,2-Dimethyl-1-(2-furanyl)butanol, (+)-2e

Resolved from alcohol **2e** (9.23 g, 54.9 mmol) by method B of Kobayashi *et al.*[12a] FC (90:10 petroleum ether:ethyl acetate) of the residue afforded (+)-**2e** (2.58 g, 28%, 93% ee): colorless oil, b.p. 63–65°C/0.8 Torr (bulb-to-bulb dest.); n_D^{20} 1.471; $[\alpha]_D^{25}$+37.8 (*c* 1.19, $CHCl_3$); IR (neat): 3600–3100, 2950, 1500; ^{1}H-NMR ($CDCl_3$): δ 0.95 (s, 9H), 1.78 (d, ^3J=5.2, 1H, ext. D_2O), 1.77 (d of *AB*q, $^3J_1$=14.2, $^3J_2$=7.4, 1H), 1.84 (d of *AB*q, $^3J_1$=14.2, $^3J_2$=5.4, 1H), 4.82 (ddd, $^3J_1$=7.4, $^3J_2$=5.4, $^3J_3$=5.2, 1H), 6.22 (dd, $^3J_1$=3.2, $^3J_2$=0.8, 1H), 6.32 (dd, $^3J_1$=3.2, $^3J_2$=1.8, 1H), 7.36 (dd, $^3J_1$=1.8, $^3J_2$=0.8, 1H); $C_{10}H_{16}O_2$ (168.2): calc. C 71.39, H 9.59, found C 71.01, H 9.36.

Esterification of alcohols 2a–f to furfuryl fumarates 3a–f (general procedure)

Method A (lithium alkanoate/carboxylic chloride, with retention)

A cooled (0°C) and stirred solution of freshly distilled alcohol **2** in Et_2O was treated with 1.0 equiv. of butyllithium (1.6 M solution in hexane). After additional stirring for 1 h at 0°C the mixture was cooled to −15°C and a solution of 1.1 equiv. of fumaroyl chloride mono methyl ester in Et_2O was added dropwise. During the addition, the temperature of the reaction mixture was not allowed to rise above −10°C. Stirring was continued for at least 3 h at ambient temperature. Then the mixture was quenched with water and extracted with Et_2O (3×). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The reddish-brown, oily residue was further purified by FC (95:5 petroleum ether:ethyl acetate). Bulb-to-bulb distillation under high vacuum was necessary to remove the solvent entirely.

Method B (Mitsunobu, with inversion)

Equimolar amounts of alcohol **2**, fumaric acid mono methyl ester and triphenylphosphine (TPP) were dissolved in an appropriate volume of THF (about 10–15 ml/mmol) under an argon atmosphere

and cooled down below +5°C. One equivalent of diethyl azodicarboxylate (DEAD) was added via syringe very slowly. When addition was completed, the solution was slightly yellow (excess of DEAD). The reaction mixture was allowed to come to room temperature and stirred for at least 12 h. The reaction was quenched by filtration through a plug of Celite®. After removal of the solvent the oily residue was purified by FC (90:10 petroleum ether:ethyl acetate). For analytical purposes, bulb-to-bulb distillation under high vacuum was necessary.

*(1S)-(E)-1-(2-Furanyl)ethyl methyl 2-butendioate, (−)-**3a***

Transformation of **(+)-2a** (270 mg, 2.4 mmol) according to method B afforded **(−)-3a** (436 mg, 81%, 98% ee) as a colorless oil, b.p.: 110°C/0.5 Torr (bulb-to-bulb dest.); $[\alpha]_D^{25}$ −8.8 (*c* 4.61, CH_2Cl_2); IR (neat): 3160, 3000, 1725, 1640, 1500; ^{1}H-NMR ($CDCl_3$): δ 1.64 (d, ^3J=6.7, 3H), 3.80 (s, 3H), 6.06 (q, ^3J=6.7, 1H), 6.35 (dd, $^3J_1$=3.3, $^3J_2$=1.6, 1H), 6.36 (dd, $^3J_1$=3.3, $^3J_2$=1.0, 1H), 6.86 (s, 2H), 7.40 (dd, $^3J_1$=1.6, $^3J_2$=1.0, 1H); $C_{11}H_{12}O_5$ (224.2): calc. C 58.92, H 5.39, found C 58.68, H 5.37.

*(1S)-(E)-1-(2-Furanyl)propyl methyl 2-butendioate, (−)-**3b***

Transformation of **(+)-2b** (631 mg, 5.0 mmol) according to method B afforded **(−)-3b** (619 mg, 52%, 99% ee) as a colorless oil, b.p.: 100°C/0.3 Torr (bulb-to-bulb dest.); $[\alpha]_D^{25}$ −14.9 (*c* 2.32, CH_2Cl_2); IR (neat): 3150, 2980, 2960, 1720, 1640, 1500; ^{1}H-NMR ($CDCl_3$): δ 0.94 (t, ^3J=7.4, 3H), 1.96–2.09 (m, 2H), 3.80 (s, 3H), 5.85 (dd, $^3J_1$=7.4, $^3J_2$=7.2, 1H), 6.34 (dd, $^3J_1$=3.4, $^3J_2$=1.8, 1H), 6.36 (dd, $^3J_1$=3.4, $^3J_2$=0.9, 1H), 6.87 (s, 2H), 7.39 (dd, $^3J_1$=1.8, $^3J_2$=0.9, 1H); $C_{12}H_{14}O_5$ (238.2): calc. C 60.50, H 5.92, found C 60.37, H 5.97.

*(1S)-(E)-1-(2-Furanyl)-2-methylpropyl methyl 2-butendioate, (−)-**3c***

Transformation of **(+)-2c** (421 mg, 3.0 mmol) according to method B afforded **(−)-3c** (439 mg, 58%, 99% ee) as a colorless oil, b.p.: 130°C/0.5 Torr (bulb-to-bulb dest.); $[\alpha]_D^{25}$ −8.5 (*c* 5.39, CH_2Cl_2); IR (neat): 3150, 2965, 1720, 1635, 1495; ^{1}H-NMR ($CDCl_3$): δ 0.87 (d, ^3J=6.9, 3H), 1.00 (d, ^3J=6.6, 3H), 2.36 (dtt, $^3J_1$=8.4, $^3J_2$=6.9, $^3J_3$=6.6, 1H), 3.80 (s, 3H), 5.63 (d, ^3J=8.4, 1H), 6.31–6.34 (m, 2H), 6.88 (s, 2H), 7.38 (dd, $^3J_1$=1.5, $^3J_2$=1.2, 1H); $C_{13}H_{16}O_5$ (252.3): calc. C 61.89, H 6.39, found C 61.47, H 6.39.

(1RS)-(E)-2,2-Dimethyl-1-(2-furanyl)propyl methyl 2-butendioate, **rac-*3d*[24]**

Transformation of ***rac*-2d** (308 mg, 2.0 mmol) according to method A afforded ***rac*-3d** (256 mg, 48%) as a colorless oil, b.p.: 140°C/0.3 Torr (bulb-to-bulb dest.); IR (neat): 3170, 2970, 1725, 1645, 1505; ^{1}H-NMR ($CDCl_3$): δ 1.00 (s, 9H), 3.81 (s, 3H), 5.63 (s, 1H), 6.27 (dd, $^3J_1$=3.2, $^3J_2$=0.8, 1H), 6.33 (dd, $^3J_1$=3.2, $^3J_2$=1.8, 1H), 6.88, 6.90 (ABq, $^3J_{AB}$=15.8, 2H), 7.36 (dd, $^3J_1$=1.8, $^3J_2$=0.8, 1H); $C_{14}H_{18}O_5$ (266.3): calc. C 63.14, H 6.81, found C 63.15, H 6.81.

*(1S)-(E)-3,3-Dimethyl-1-(2-furanyl)butyl methyl 2-butendioate, (−)-**3e***

Transformation of **(+)-2e** (841 mg, 5.0 mmol) according to method B afforded **(−)-3e** (575 mg, 41%, 93% ee) as a colorless oil, b.p.: 100°C/0.1 Torr (bulb-to-bulb dest.); $[\alpha]_D^{25}$ −15.2 (*c* 1.19, CH_2Cl_2); IR (neat): 3150, 2960, 2910, 1725, 1640, 1500; ^{1}H-NMR ($CDCl_3$): δ 0.91 (s, 9H), 1.98 (d, ^3J=6.7, 2H), 3.79 (s, 3H), 6.07 (t, ^3J=6.7, 1H), 6.32 (dd, $^3J_1$=3.3, $^3J_2$=1.7, 1H), 6.34 (dd, $^3J_1$=3.3, $^3J_2$=1.0, 1H), 6.84 (s, 2H), 7.38 (dd, $^3J_1$=1.7, $^3J_2$=1.0, 1H); $C_{15}H_{20}O_5$ (280.3): calc. C 64.27, H 7.19, found C 64.01, H 7.29.

*(1R)-(E)-1-(2-Furanyl)-1-phenylmethyl methyl 2-butendioate, (+)-**3f***

This diester turned out to be very unstable, especially during chromatographic workup. As a result **(+)-3f** was prepared according to method A from **(+)-2f**, but not isolated in pure form. Instead the

crude product resulting after concentrating the organic extracts was immediately cyclized under high pressure (*vide infra*).

Cyclization of IMDA precursors 3 to adducts 4 and 5[25]

(a) High-pressure induced cycloaddition

About 1–2 mmol furfuryl fumarate **3** were dissolved in 7–8 ml dry acetone that had been saturated with argon. This solution was completely transferred into a flexible teflon tube which is stoppered at both sides by stainless steel plugs. This reaction vessel was immersed into a 1:1 mixture of decaline and isooctane, used as piezotransmitter liquid which was contained in the high-pressure apparatus. The reaction was routinely performed at 7 kbar and 40°C for 18 h. After decompression the solvent was removed and the residue analyzed by ^{1}H-NMR (400 MHz). The cycloadducts were purified by FC using mixtures of petroleum ether–ethyl acetate. Recrystallization from methanol normally yielded in 1–2 steps the major adduct in enantiomerically pure form (except for **4a**, R=Me).

(b) Thermally induced cycloaddition

About 0.2 mmol furfuryl fumarate **3** were dissolved in 0.4 ml dry [d_6] acetone in a NMR probe tube and reacted at 40°C for several days. The reaction was monitored by ^{1}H-NMR. After equilibration the solvent was removed and the residue was finally analyzed by ^{1}H-NMR (400 MHz). Further workup however was suspended because of the unfavorable starting material:product ratio.

(3S,3aS,6R,7R,7aR)-Methyl 1,6,7,7a-tetrahydro-3-methyl-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, ***4a***[26]

Colorless crystals, m.p.: 123–124°C; IR (KBr): 3100, 2960, 2860, 1770, 1730; ^{1}H-NMR ($CDCl_3$): δ 1.48 (d, ^3J=6.62, 3H), 3.11 (d, ^3J=3.38, 1H), 3.57 (dd, $^3J_1$=3.38, $^3J_2$=4.81, 1H), 3.69 (s, 3H), 5.11 (q, ^3J=6.62, 1H), 5.34 (dd, $^3J_1$=4.81, $^3J_2$=1.62, 1H), 6.39 (dd, $^3J_1$=5.94, $^3J_2$=1.62, 1H), 6.56 (d, ^3J=5.94, 1H); $C_{11}H_{12}O_5$ (224.2): calc. C 58.93, H 5.39, found C 58.18, H 5.71.

(3S,3aS,6R,7R,7aR)-Methyl 1,6,7,7a-tetrahydro-3-ethyl-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, ***4b***

Colorless crystals, m.p.: 113–114°C; IR (KBr): 3140, 2970, 2940, 2880, 1770, 1730; ^{1}H-NMR ($CDCl_3$): δ 1.05 (t, ^3J=7.45, 3H), 1.74–2.01 (m, 2H), 3.10 (d, ^3J=3.44, 1H), 3.54 (dd, $^3J_1$=4.80, $^3J_2$=3.44, 1H), 3.69 (s, 3H), 4.85 (dd=t, ^3J=7.3, 1H), 5.33 (dd, $^3J_1$=4.80, $^3J_2$=1.60, 1H), 6.35 (dd, $^3J_1$=5.85, $^3J_2$=1.60, 1H), 6.58 (d, ^3J=5.85, 1H); $C_{12}H_{14}O_5$ (238.2): calc. C 60.49, H 5.92, found C 60.52, H 5.97.

(3S,3aS,6R,7R,7aR)-Methyl 1,6,7,7a-tetrahydro-3-(1-methylethyl)-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, ***4c***

Colorless crystals, m.p.: 123–124°C; IR (KBr): 3140, 3100, 2980, 2960, 2890, 1775, 1740; ^{1}H-NMR ($CDCl_3$): δ 0.95 (d, ^3J=6.76, 3H), 1.15 (d, ^3J=6.59, 3H), 2.04–2.17 (m, 1H), 3.10 (d, ^3J=3.43, 1H), 3.53 (dd, $^3J_1$=4.81, $^3J_2$=3.43, 1H), 3.69 (s, 3H), 4.49 (d, ^3J=10.04, 1H), 5.32 (dd, $^3J_1$=4.81, $^3J_2$=1.64, 1H), 6.31 (dd, $^3J_1$=5.80, $^3J_2$=1.64, 1H), 6.58 (d, ^3J=5.80, 1H); $C_{13}H_{16}O_5$ (252.3): calc. C 61.89, H 6.39, found C 61.63, H 6.27.

(3S,3aS,6R,7R,7aR)-Methyl 1,6,7,7a-tetrahydro-3-(1,1-dimethylethyl)-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, ***4d*** *+ enantiomer*

Colorless crystals, m.p.: 124–125°C; IR (KBr): 3160, 3110, 2980, 2950, 2890, 1775, 1740; ^{1}H-NMR ($CDCl_3$): δ 1.08 (s, 9H), 3.08 (d, ^3J=3.51, 1H), 3.50 (dd, $^3J_1$=4.86, $^3J_2$=3.51, 1H), 3.69 (s, 3H), 4.59 (s, 1H), 5.32 (dd, $^3J_1$=4.86, $^3J_2$=1.76, 1H), 6.28 (dd, $^3J_1$=5.81, $^3J_2$=1.76, 1H), 6.58 (d, ^3J=5.81, 1H); NOE: 4.59→ 1.08, 3.08, 6.58; $C_{14}H_{18}O_5$ (266.3): calc. C 63.15, H 6.81, found C 63.16, H 6.83.

(3S,3aS,6R,7R,7aR)-Methyl 1,6,7,7a-tetrahydro-3-(2,2-dimethylpropyl)-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, ***4e***

Colorless crystals, m.p.: 129–130°C; IR (KBr): 3140, 3100, 2960, 2900, 1770, 1740; ^{1}H-NMR ($CDCl_3$): δ 1.02 (s, 9H), 1.62 (d of A*B*q, $^3J_1$=15.30, $^3J_2$=9.10, 1H), 1.78 (d of *A*Bq, $^3J_1$=15.30, $^3J_2$=2.46, 1H), 3.07 (d, ^3J=3.35, 1H), 3.56 (dd, $^3J_1$=4.88, $^3J_2$=3.35, 1H), 3.69 (s, 3H), 5.03 (dd, $^3J_1$=9.10, $^3J_2$=2.46, 1H), 5.31 (dd, $^3J_1$=4.88, $^3J_2$=1.60, 1H), 6.38 (dd, $^3J_1$=5.78, $^3J_2$=1.60, 1H), 6.55 (d, ^3J=5.78, 1H); NOE: 5.31 → 3.56, 6.38 (3.07, 3,69, 6.55), 3.07 → 3.56, 5.03, 6.55 (3.69, 5.31, 6.38); $C_{15}H_{20}O_5$ (280.3): calc. C 64.27, H 7.19, found C 64.01, H 7.18.

Cycloadducts of furfuryl fumarate (+)-3f[27]

The crude product of esterification of (+)-**2f** (730 mg, 4.2 mmol) with (*E*)-β-carbomethoxyacryloyl chloride (624 mg, 4.2 mmol) according to method A[28] was reacted at 7.4 kbar and 40°C for 18 h. After decompression the solvent was removed and the black, oily residue was analyzed by ^{1}H-NMR (400 MHz). It turned out that the cycloaddition was complete, yielding a mixture of diastereomers in a 77:23 ratio (54% de) with no starting material left. Carefully carried out flash chromatography (95:5 petroleum ether:ethyl acetate) provided 100 mg of the minor adduct *epi*-**4f** (8%), 390 mg of the major adduct *epi*-**5f** (32%), and 100 mg of a mixed fraction. Yields went low because the open chain compound **3f** tends to decompose on silica gel and there is a rapid equilibrium between **3f** and the cycloadducts *epi*-**4f** and *epi*-**5f** probably due to silica catalysis. Fortunately the major adduct *epi*-**5f** could be further purified by recrystallization in methanol (3×). However the minor adduct *epi*-**4f** decomposes too fast.

(3R,3aR,6S,7S,7aS)-Methyl 1,6,7,7a-tetrahydro-3-phenyl-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, **epi-5f**

Colorless crystals, m.p.: 129–130°C; IR (KBr): 3150, 3110, 3070, 3045, 2950, 2840, 1765, 1730, 1490; ^{1}H-NMR: δ 3.28 (d, ^3J=3.37, 1H), 3.63 (dd, $^3J_1$=4.85, $^3J_2$=3.37, 1H), 3.69 (s, 3H), 5.28 (dd, $^3J_1$=4.85, $^3J_2$=1.62, 1H), 6.04 (s, 1H), 6.37 (dd, $^3J_1$=5.85, $^3J_2$=1.62, 1H), 6.72 (d, ^3J=5.85, 1H), 7.31–7.46 (m, 5H); NOE: 6.04 → 3.28, 6.39, 6.75; $C_{16}H_{14}O_5$ (286.3): calc. C 67.12, H 4.93, found C 66.75, H 4.99.

(3R,3aS,6R,7R,7aR)-Methyl 1,6,7,7a-tetrahydro-3-phenyl-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, **epi-4f**

^{1}H-NMR: δ 3.15 (d, ^3J=3.34, 1H), 3.61 (dd, $^3J_1$=4.79, $^3J_2$=3.34, 1H), 3.67 (s, 3H), 5.36 (dd, $^3J_1$=4.79, $^3J_2$=1.60, 1H), 5.81 (s, 1H), 6.11 (d, ^3J=5.87, 1H), 6.28 (dd, $^3J_1$=5.87, $^3J_2$=1.60, 1H), 7.37–7.50 (m, 5H); NOE: 5.81 → 6.11, 6.28, (5.36, 3.15).

Synthesis of IMDA precursor ***10*** *and cycloadduct* ***11***

Reduction of methyl 3-methyl-2-furoate ***6*** *with LAH 2-(3-methyl)furanylmethanol* ***7***

Methyl 3-methyl-2-furoate **6** (35.63 g, 250 mmol) was dissolved in Et_2O (100 ml) and added dropwise to a cooled (0°C) suspension of $LiAlH_4$ (5.22 g, 137.5 mmol) in a 1:1 mixture of Et_2O and THF (250 ml). The reaction mixture was allowed to warm up to room temperature with continued stirring. After 4 h all of the starting material had reacted as indicated by TLC. The reaction mixture was cooled again and quenched cautiously with cold water (150 ml). Some basic precipitate that had formed was redissolved by the addition of 10% sulfuric acid. The aqueous phase was saturated with NaCl, followed by extraction with Et_2O (3×100 ml). The organic phases were combined, washed with brine, dried (Na_2SO_4) and evaporated to give alcohol **7** as a dark green oil (27.9 g, 100%). To our surprise, during further purification, for example, by destillation *in vacuo*, **7** turned out to be very unstable even under an argon atmosphere. Therefore we decided to use only the crude product for the following synthetic steps. b.p.: 47–48°C/0.2 Torr; n_D^{20} 1.373; IR (neat): 3700–3100, 2940, 2880,

1510, 1010; ^{1}H-NMR ($CDCl_3$): δ 2.00 (s, 3H), 2.20 (bs, 1H, ext. D_2O), 4.53 (s, 2H), 6.17 (d, ^3J=2.1, 1H), 7.27 (d, ^3J=2.1, 1H).

Oxidation of 2-(3-methyl)furanylmethanol 7 with active manganese dioxide: 3-methylfurfuraldehyde 8

A solution of crude 2-(3-methyl)furanylmethanol **7** (17.30 g, 154 mmol) in CH_2Cl_2 (100 ml) was added dropwise to active manganese dioxide (71.30 g, 820 mmol, 5.3 equiv.) suspended in dry CH_2Cl_2 (1200 ml) under vigorous stirring at 20°C. After addition was completed, stirring was continued for an additional 6 h at ambient temperature before the reaction mixture was filtered through Celite® and concentrated *in vacuo* giving a reddish-brown, oily residue. FC (95:5 petroleum ether:ethyl acetate) provided **8** (3.23 g, 19%) as a colorless oil, b.p.: 48–50°C/0.5 Torr; n_D^{20} 1.521; IR (neat): 3140, 2940, 2870, 2830, 1670, 1580; ^{1}H-NMR ($CDCl_3$): 2.40 (s, 3H), 6.43 (d, ^3J=1.5, 1H), 7.56 (d, ^3J=1.5, 1H), 9.77 (s, 1H); $C_6H_6O_2$ (110.1): calc. C 65.45, H 5.49, found C 64.70, H 5.70.

Grignard addition of MeMgJ to 8: (1RS)-1-[2-(3-methyl)furanyl]ethanol, **rac-9**

A solution of 3-methylfurfuraldehyde **8** (6.41 g, 58.2 mmol) in Et_2O (70 ml) was slowly added to a cooled (0°C) suspension of MeMgJ, prepared from MeJ (4.36 ml, 69.8 mmol) in 100 ml Et_2O. The cooling bath was removed and the reaction mixture refluxed for 1 h. Then the reaction was quenched by the addition of aqueous NH_4Cl. The organic layer was separated and the aqueous phase extracted with Et_2O (3×50 ml). The combined organic phases were successively washed with saturated aqueous bisulfite (2×), $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The oily residue was further purified by bulb-to-bulb destillation yielding *rac*-**9** (6.01 g, 82%) as a colorless liquid: b.p.: 70–80°C/0.4 Torr (bulb-to-bulb dest.); IR (neat): 3600–3100, 2970, 2930, 2870, 1500; ^{1}H-NMR ($CDCl_3$): δ 1.78 (bd, ^3J=3.2, 1H, ext. D_2O), 2.05 (s, 3H), 4.92 (dq, $^3J_1$=6.3, $^3J_2$=3.1, 1H), 6.18 (d, ^3J=1.7, 1H), 7.27 (d, ^3J=1.7, 1H); $C_7H_{10}O_2$ (126.2): calc. C 66.65, H 7.99, found C 66.02, H 7.86.

(1R)-1-[2-(3-Methyl)furanyl]ethanol, (+)-9

Alcohol **9** (2.66 g, 21.1 mmol) was enantiomerically enriched by Sharpless oxidation with a stoichiometric amount of Ti(O*i*Pr)$_4$ (6.21 ml, 21.1 mmol) and *L*-(+)-DIPT (5.97 g, 25.5 mmol, 1.2 equiv.). The reaction time (2.5 h) was modified compared with the reported oxidation of 1-[2-(3-methyl)furanyl]hexanol[12a] having a reaction time of 4 h. The mediocre enantioselectivity of the Sharpless kinetic resolution in this case therefore may have been the result of stopping the reaction too early. The crude product was purified by FC (90:10 petroleum ether:ethyl acetate) and bulb-to-bulb distillation yielding **(+)-9** (1.00 g, 38%, 85% ee) as a colorless liquid. $[\alpha]_D^{20}$ +34.6 (*c* 2.27, $CHCl_3$); $C_7H_{10}O_2$ (126.2): calc. C 66.65, H 7.99, found C 65.45, H 7.92.

Esterification of (+)-9 with fumaric acid mono methyl ester

(1*R*)-1-[2-(3-Methyl)furanyl)ethanol **(+)-9** (1.26 g, 10.0 mmol) in dry THF (20 ml) was treated with fumaric acid mono methyl ester (1.30 g, 10.0 mmol, 1.0 equiv.), TPP (2.62 g, 10.0 mmol) and DEAD (1.57 ml, 10.0 mmol) according to method B as described above. After stirring at room temperature for 18 h the reaction mixture was filtered through a pad of Celite® and the solvent removed. Since the crude product turned out to be very unstable this operation was executed under an argon atmosphere in a Schlenk flask. The sticky, pink-colored residue was flash chromatographied with mixtures of petroleum ether–ethyl acetate. Two fractions were isolated, first the expected diester **(−)-10** (120 mg, 5%) as a colorless oil, secondly as the main product the IMDA adduct **11** (900 mg, 38%).

(1S)-(E)-1-[2-(3-Methyl)furanyl]ethyl methyl 2-butendioate, ***10***

A very unstable, colorless oil which tends to cyclize even at +4°C, sensible to light and oxygen. The ORD spectra could not be determined as cyclization took place immediately. IR (CCl_4): 2990,

2950, 2860, 1720, 1640; ^{1}H-NMR ($CDCl_3$): δ 1.63 (d, ^3J=6.8, 1H), 2.08 (s, 3H), 3.79 (s, 3H), 6.06 (q, ^3J=6.8, 1H), 6.20 (d, ^3J=1.8, 1H), 6.85 (s, 2H), 7.31 (d, ^3J=1.8, 1H).

(3S,3aS,6R,7R,7aR)-Methyl 1,6,7,7a-tetrahydro-3,4-dimethyl-1-oxo-3H-3a,6-epoxyisobenzofuran-7-carboxylate, 11

Colorless crystals, m.p.: 98–100°C (from MeOH); IR (KBr): 3110, 2960, 2940, 2860, 1765, 1740; ^{1}H-NMR ($CDCl_3$): δ 1.46 (d, ^3J=6.54, 3H), 1.91 (d, ^3J=1.82, 3H), 3.07 (d, ^3J=3.54, 1H), 3.57 (dd, $^3J_1$=4.67, $^3J_2$=3.54, 1H), 3.69 (s, 3H), 5.04 (q, ^3J=6.54, 1H), 5.21 (ddq, $^3J_1$=4.67, $^3J_2$=1.70, $^3J_3$=0.50, 1H), 5.93 (dq, $^3J_1$=1.82, $^3J_2$=1.70, 1H); NOE: 5.04 → 1.46, 1.91, 3.07; 3.07 → 1.91, 5.04, (5.93); 1.91 → 1.46, 3.07, 5.04, 5.93; 1.46 → (1.91), 5.04; $C_{10}H_{14}O_5$ (238.5): calc. C 60.49, H 5.92, found C 60.28, H 6.04.

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24. Alcohol **2d** could not be prepared in enantiomerically pure form, so the racemic form was used.

25. The optical rotations of compounds **4a–e** and **5f** were too small to be determined in an accurate manner.
26. ^{1}H-NMR data for the minor adducts **5a–e**: **(3*S*,3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-tetrahydro-3-methyl-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate, 5a:** δ 1.62 (d, ^3J=6.75, 3H), 3.10 (d, ^3J=3.37, 1H), 3.55 (dd, $^3J_1$=3.37, $^3J_2$=4.86, 1H), 3.70 (s, 3H), 4.90 (q, ^3J=6.89, 1H), 5.32 (dd, $^3J_1$=4.86, $^3J_2$=1.62, 1H), 6.39 (dd, $^3J_1$=5.94, $^3J_2$=1.62, 1H), 6.58 (d, ^3J=5.94, 1H). **(3*S*,3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-tetrahydro-3-ethyl-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate, 5b:** δ 1.18 (t, ^3J=7.40, 3H), 1.77–2.07 (m, 2H), 3.05 (d, ^3J=3.33, 1H), 3.54 (dd, $^3J_1$=4.80, $^3J_2$=3.33, 1H), 3.70 (s, 3H), 4.67 (dd, $^3J_1$=9.22, $^3J_2$=4.43, 1H), 5.30 (dd, $^3J_1$=4.80, $^3J_2$=1.60, 1H), 6.39 (dd, $^3J_1$=5.85, $^3J_2$=1.60, 1H), 6.59 (d, ^3J=5.85, 1H). **(3*S*,3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-tetrahydro-3-(1-methylethyl)-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate, 5c:** δ 1.09 (d, ^3J=6.84, 3H), 1.44 (d, ^3J=6.84, 3H), 2.17–2.27 (m, 1H), 3.03 (d, ^3J=3.48, 1H), 3.51 (dd, $^3J_1$=4.81, $^3J_2$=3.48, 1H), 3.70 (s, 3H), 4.56 (d, ^3J=4.93, 1H), 5.28 (dd, $^3J_1$=4.81, $^3J_2$=1.65, 1H), 6.40 (dd, $^3J_1$=5.91, $^3J_2$=1.65, 1H), 6.65 (d, ^3J=5.91, 1H). **(3*S*,3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-tetrahydro-3-(1,1-dimethylethyl)-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate, 5d+enantiomer**: δ 1.14 (s, 9H), 3.03 (d, ^3J=3.51, 1H), 3.51 (dd, $^3J_1$=4.87, $^3J_2$=3.51, 1H), 3.70 (s, 3H), 4.40 (s, 1H), 5.24 (dd, $^3J_1$=4.87, $^3J_2$=1.62, 1H), 6.39 (dd, $^3J_1$=5.94, $^3J_2$=1.62, 1H), 6.75 (d, ^3J=5.94, 1H). **(3*S*,3a*R*,6*S*,7*S*,7a*S*)-Methyl 1,6,7,7a-tetrahydro-3-(2,2-dimethylpropyl)-1-oxo-3*H*-3a,6-epoxyisobenzofuran-7-carboxylate, 5e**: δ 1.07 (s, 9H), 1.71 (d of A*B*q, $^3J_1$=14.52, $^3J_2$=10.95, 1H), 1.80 (d of *A*Bq, $^3J_1$=14.52, $^3J_2$=2.58, 1H), 3.05 (d, ^3J=3.32, 1H), 3.55 (dd, $^3J_1$=4.92, $^3J_2$=3.32, 1H), 3.69 (s, 3H), 4.88 (dd, $^3J_1$=10.95, $^3J_2$=2.58, 1H), 5.30 (dd, $^3J_1$=4.92, $^3J_2$=1.72, 1H), 6.38 (dd, $^3J_1$=5.91, $^3J_2$=1.72, 1H), 6.58 (d, ^3J=5.91, 1H).
27. The prefix *epi* must have been introduced for the inverted stereochemistry at C-3 in adducts **4f** and **5f** since the *dextrorotatory* furfuryl fumarate (+)-**3f** was utilized.
28. Stirring time at room temperature was shortened to 2 h because of the apparent instability of the diester intermediate.

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