Simple Synthetic Transformations of Highly Enantio-Enriched 4-Alkyl-2,5,7-cyclooctatrienols into Functionalized Bicyclo[4.2.0]octa-2,4-dienes and 2,6-Cyclooctadienones

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4-Alkyl-2,5,7-cyclooctatrienols with high enantiomeric purities (93–96% *ee*), obtained by an improved copper-phosphoramidite-catalyzed addition of dialkylzinc reagents to cyclooctatetraene monoepoxide, have been subjected to simple and practical manipulations. Simple esterification reactions are able to deliver new functionalized isomeric 8-alkyl-7-acyloxybicyclo[4.2.0]octa-2,4-dienes through a domino sequence of rearrangement reactions, in good yields. Moreover, new 4-alkyl-substituted-2,6-cyclooctadienones with high optical purity can be efficiently obtained from gram-scale reactions by simple thermal treatment.

Introduction

The bicyclo[4.2.0]octane moiety is a structural feature that is present in many naturally occurring molecules;[1,2] bicyclo[4.2.0]octa-2,4-dienes, in particular, have been known for a long time.[3,4] The conversion of cyclooctatetraenes into cycloocta-1,3,5-trienes, and subsequently to bicyclo[4.2.0]octa-2,4-dienes, is an interesting stereospecific series of electrocyclic reactions.[5,6] However, compounds containing the bicyclo[4.2.0]octa-2,4-diene framework, including natural products, are chiral but are usually found in a racemic form. For example, endiandric acids are natural polycyclic molecules that contain this framework. However, despite the presence of eight asymmetric centers, they occur in nature in a racemic form, and are formed from an achiral precursor by a series of non-enzymatic electrocyclizations.[7]

The development of simple and efficient routes to functionalized enantio-enriched medium-sized carbocycles is a worthy endeavor due to the presence of such systems in many biologically active and structurally interesting natural products.[8] There are a few reports on the synthesis of non-racemic cyclooctadienones — these methods are based on the use of a chiral-pool approach.[9] In particular, substituted 2,6-cyclooctadienones have been obtained only by the reaction of cyclobutenones with dienyllithiums.[10] To the best of our knowledge, the asymmetric synthesis of substituted 2,6-cyclooctadienones has not been reported to date.

We report here some novel and practical syntheses of various new, non-racemic, chiral functionalized isomeric 8-alkyl-7-acyloxybicyclo[4.2.0]octa-2,4-dienes and new 4-alkyl-substituted 2,6-cyclooctadienones by simple transformations of alkylcyclooctatrienols of high enantiomeric purity.

Results and Discussion

We have recently reported that 1,3,5,7-cyclooctatetraene (COT) monoepoxide (**1**), despite its non-planar tub form, can be successfully alkylated with appropriate organocopper reagents, such as cyanocuprates, without the occurrence of any ring-contraction isomerization.[11] The enantioselective desymmetrization reaction of compound **1** was based on the use of dialkylzinc reagents and a chiral copper complex containing the phosphoramidite (*R*,*S*,*S*)-**2** developed by Feringa et al. (Scheme 1).[12]

The dihedral angle of about 60° present between the π-orbital of the double bond and the σ-bond connecting the leaving group (the allylic oxirane bond) represents the largest deviation from coplanarity in any allylic substitution reaction.[13] From a synthetic point of view, the possibility to access previously unobtainable 4-alkyl-2,5,7-cyclooctatrienols of type **4** allowed us to study their reactivity for the first time.[14] We report here an improved preparation of 4-alkyl-2,5,7-cyclooctatrienols of type **4** in the presence of the phosphoramidite ligand (*R*,*R*,*R*)-**3**.[15] With this catalyst the enantioselective desymmetrization reaction of **1** can be performed on a gram scale with higher yields and enantio-

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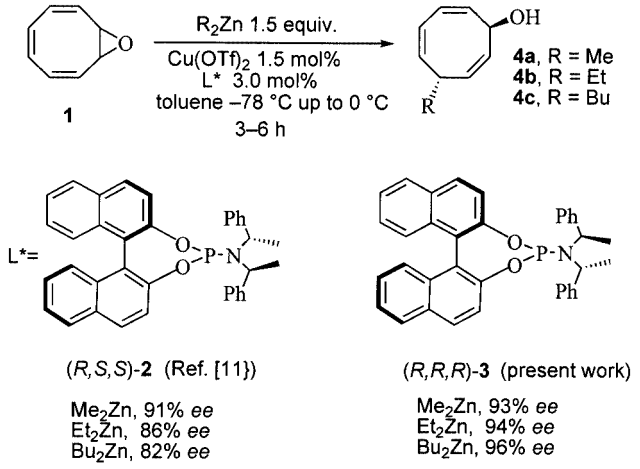


Scheme 1. Copper-phosphoramidite-catalyzed enantioselective desymmetrization of COT monoepoxides with dialkylzincs

Table 1. Results of the esterification reaction of compounds **4a**–**c** in accordance with protocols A (R^1COCl/Py) and B (R^1COOH/DCC)

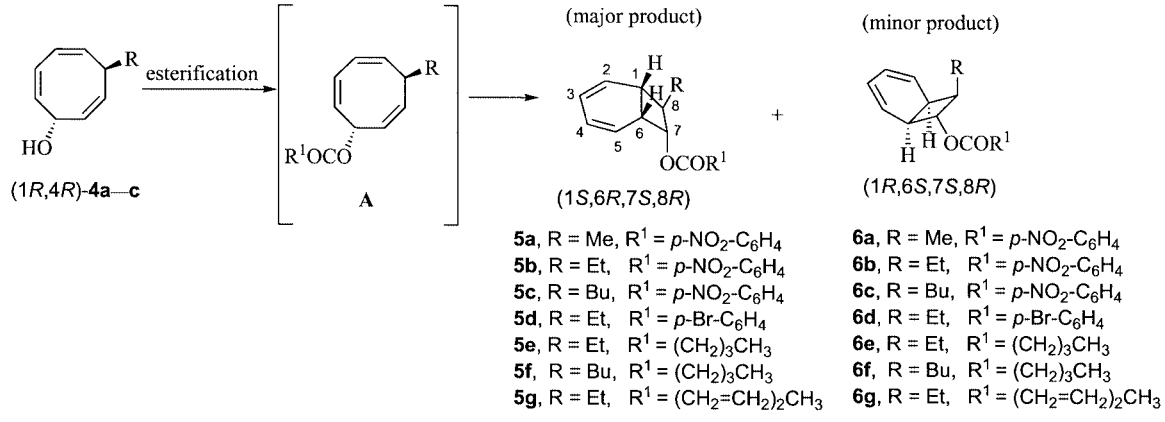
Entry	Substrate	Reaction protocol[a]	R^1	Products (ratio)[b]	Yields (%)[c]
1	**4a**	A	*p*-NO_2-C_6H_4	**5a/6a** (78:22)	36
2	**4b**	A	*p*-Br-C_6H_4	**5d/6d** (82:18)	42
3	**4b**	A	*p*-NO_2-C_6H_4	**5b/6b** (75:25)	46
4	**4b**	B	*p*-NO_2P-C_6H_4	**5b/6b** (74:26)	83
5	**4c**	B	*p*-NO_2-C_6H_4	**5c/6c** (74:26)	80
6	**4b**	B	$CH_3(CH_2)_3$	**5e/6e** (86:14)	90
7	**4c**	B	$CH_3(CH_2)_3$	**5f/6f** (86:14)	88
8	**4b**	B	$CH_3(CH{=}CH)_2$	**5g/6g** (83:17)	65

[a] All reactions were carried out in accordance with the reaction protocols A and B described in the Exp. Sect. In all cases substrate conversions were >98%. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yields of the diastereoisomeric mixture after chromatographic purification on SiO_2.

selectivities (*ee* ≥ 93%) than in our previous report (Scheme 1).[11]

The *trans*-4-alkyl-2,5,7-cyclooctatrienols **4a**–**c** obtained by our procedure can be purified by chromatography on SiO_2, albeit with partial decomposition, and it is possible to store them for several days at +5 °C. Whenever a simple derivatization of these compounds with a common acylating agent (for example R^1COCl/Py) was attempted, the corresponding eight-membered esters of type **A** were never obtained (Scheme 2). For example, when ethylcyclooctatrienol [(1*R*,4*R*)-**4b**] was treated with *p*-nitrobenzoyl chloride in anhydrous pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP; protocol A), a clean rearrangement reaction occurred to give 8-ethyl-7-(*p*-nitrobenzoyloxy)bicyclo[4.2.0]octa-2,4-dienes **5b** and **6b** (46% combined yield after chromatography) as a 75:25 mixture of isomers (Scheme 2 and entry 3, Table 1).

Moderate yields were also obtained with the methyl-substituted cyclooctatrienol **4a** (entry 1) and by using protocol A with *p*-bromobenzoyl chloride and compound **4b** (entry 2). The esterification reactions can be more conveniently performed with RCOOH/dicyclohexyl carbodiimide (DCC)/DMAP in CH_2Cl_2 at room temp. (protocol B). In this way, compounds **4a**–**c** were cleanly transformed into the corresponding *trans*-8-alkyl-7-acyloxybicyclo[4.2.0]-octa-2,4-dienes (1*S*,6*R*,7*R*,8*S*)-**5a**–**g** and (1*R*,6*S*,7*R*,8*S*)-**6a**–**g**, with higher yields and a more simple workup procedure (entries 4–8, Table 1). Compounds of type **5a**–**g**, bearing the alkyl group on the same side as the hydrogen on the bridgeheads, always constituted the major reaction product (74–86% of the crude mixture) after the esterification reaction and workup procedures. It should be noted that related racemic *cis*- and *trans*-8-methyl-7-acetoxybicyclo[4.2.0]octa-2,4-dienes (R = R^1 = Me) have been obtained to date only by electrochemical oxidation of COT in acetic acid containing the acetate ion (3% yield).[16] Our new approach provides a general entry to non-racemic *trans*-7-acyloxy-8-alkylbicyclo[4.2.0]octa-2,4-dienes, albeit as a mixture of diastereoisomers. It is likely that the mixtures of bicyclic compounds **5** and **6** are obtained under thermodynamic control, as each isomerically pure bicyclo[4.2.0] compound **5a**–**g** or **6a**–**g**, when allowed to stand for several hours in a solvent, undergoes an equilibration reaction affording approximately the product ratio indicated in Table 1.



Scheme 2. Synthesis of functionalized 8-alkyl-7-acyloxybicyclo[4.2.0]octa-2,4-dienes by esterification reactions

As a consequence of this rapid equilibration process, the NMR spectroscopic data for the pure isomeric compounds had to be recorded rapidly in order to minimize the corresponding isomerization reactions.[17] The relative stereochemistry of bicyclo[4.2.0] compounds **5a**−**g** or **6a**−**g** was unambiguously demonstrated by the NOEs observed in ROESY experiments. For example, after chromatographic separation of the mixture by preparative TLC, compounds **5a** and **6b** were rapidly subjected to ROESY experiments and it was found that the alkyl group on C^8 and the oxygenated group on C^7 were invariably in a *trans* relationship in both isomers. In the most abundant isomer **5b**, there is a strong NOE between H^1/H^6 and the methylene protons of the ethyl substituent in C^8 (Figure 1). The absence of a corresponding NOE between H^1/H^6 and the methylene protons of the ethyl substituent in C^8 suggests that these hydrogens are not on the same face in the minor isomer **6b**. In this isomer a strong NOE effect between H^1/H^6 and H^8 across the cyclobutane ring is observed, indicating that all these hydrogens are on the convex face. The absolute *R* configuration of C(8) of compounds **4a**−**c**, which is maintained in the rearranged bicyclic compounds **5** and **6** (vide infra), has been previously demonstrated by catalytic hydrogenation of the three double bonds to the corresponding saturated enantiomerically enriched 4-alkylcyclooctanols.[11]

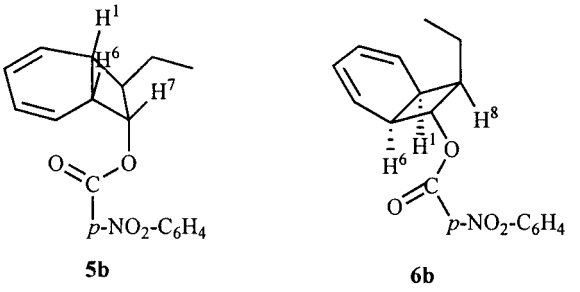
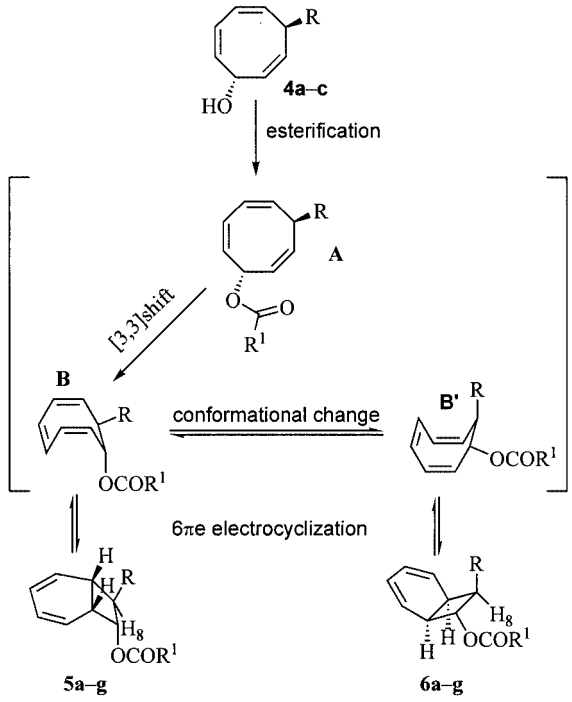


Figure 1. Determination of relative stereochemistry by the NOEs observed in ROESY experiments

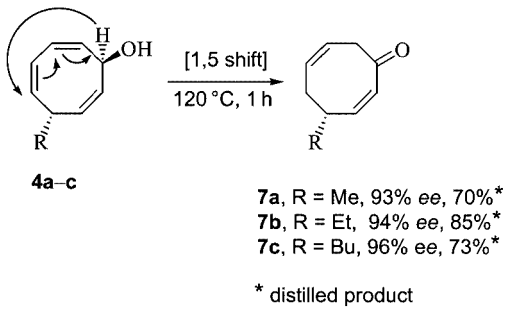
It is likely that the esterification of alcohols **4a**−**c** is the first step of a sequence of reactions which, starting from **A**, has as the first step a [3,3]-sigmatropic rearrangement[18] with full involvement of the carbonyl oxygen to a presumed 1-acyloxy-2-alkyl-3,5,7-cyclooctatriene, which exists as an equilibrating mixture of conformers **B** and **B′** (Scheme 3).[19] Each conformer can undergo a disrotatory 6π-electron electrocyclization to give a mixture of bicyclo[4.2.0]octa-2,4-dienes (1*S*,6*R*,7*R*,8*S*)-**5a**−**g** and (1*R*,6*S*,7*R*,8*S*)-**6a**−**g**. A back-opening of **5a**−**g** and **6a**−**g** to the corresponding cyclooctatetraenes **B** and **B′** can then occur to give the final thermodynamic product distribution.[20]

During our study we found that the obtained *trans*-4-alkyl-2,5,7-cyclooctatrienols **4a**−**c** are not stable to thermal treatment. When purification of compounds **4a**−**c** was attempted by distillation rather than by standard chromatographic purification, most of the substance isomerized and the corresponding new 4-alkyl-2,6-cyclooctadien-1-ones



Scheme 3. Proposed mechanism for the formation of functionalized bicyclo[4.2.0]octa-2,4-dienes

7a−**c** were obtained with high yields. It is known that 2,4-cyclooctadien-1-ol thermally rearranges into cycloocta-3-en-1-one by a 1,5-hydrogen shift.[21] Furthermore, the formation of racemic 4-*tert*-butylcycloocta-2,6-diene-1-one by the reaction of *t*BuLi with COT monoepoxide and subsequent distillation has been described, albeit without the isolation of the intermediate 4-*tert*-butyl-2,5,7-cyclooctatriene-1-ol.[22] In our hands the rearrangement of isolated crude 4-alkyl-2,5,7-cyclooctatriene-1-ols to new 4-alkyl-2,6-cyclooctadien-1-ones **7a**−**c** has been easily and thoroughly accomplished by means of a simple pre-treatment of the crude mixture containing cyclooctatrienes **4a**−**c** with refluxing toluene for 1 h followed by vacuum distillation (Scheme 4). For example, with this procedure it was possible to obtain enantiomerically enriched (4*R*)-**7b** (94% *ee*, 85% distilled yield) from a gram-scale reaction. Similar results were obtained with simple thermal treatment of compound **4a** to give **7a** (93% *ee*, 70% distilled yield) and **4c** to give **7c** (96% *ee*, 73% distilled yield; Scheme 4). Considering



Scheme 4. Synthesis of enantio-enriched 4-alkyl-2,6-cyclooctadienones by thermally induced 1,5-sigmatropic shifts

that the enantiomers of compounds **7a−c** are very easily separated by HPLC on a chiral stationary phase (Daicel Chiralcel OB-H), this procedure provides a fast and reliable method for the determination of optical purities of compounds **4a−c**.[23] 4-Alkyl-2,6-cyclooctadienones with a high optical purity are interesting new building blocks because the presence of two different double bonds allows for further manipulations.

Conclusions

In conclusion, the present work reports an improved preparation of enantiomerically enriched 4-alkyl-2,5,7-cyclooctatrienols by a copper phosphoramidite-catalyzed addition of Me_2Zn, Et_2Zn and Bu_2Zn to COT monoepoxide **1**, as well as some simple synthetic transformations of this almost unexplored class of compounds. Simple esterification reactions afforded a mixture of new functionalized isomeric bicyclo[4.2.0]octa-2,4-dienes through a novel domino sequence of a [3,3]-sigmatropic shift and a 6π electron disrotatory electrocyclization. Moreover, the exploitation of a thermally induced [1,5]-sigmatropic shift is able to give a practical and flexible access to new 4-alkyl-2,6-cyclooctadienones with high optical purity (93−96% *ee*).

Experimental Section

General Remarks: All reactions were conducted in flame-dried glassware with magnetic stirring under an atmosphere of argon. Toluene, diethyl ether and THF were distilled from sodium/benzophenone ketyl and stored under argon. The following compounds are commercially available and were used without purification: 1,3,5,7-cyclooctatetraene (COT), MCPBA (70%), Me_2Zn (2.0 M solution in toluene), Et_2Zn (1.1 M solution in toluene), Bu_2Zn (1.0 M solution in heptane), EtMgBr (3.0 M solution in Et_2O), MeMgBr (3.0 M in Et_2O), BuMgCl (2.0 M in Et_2O), $Cu(OTf)_2$, CuCN, pentanoic acid and sorbic acid. *p*-Nitrobenzoyl chloride and *p*-bromobenzoyl chloride were recrystallized before use. The COT monoepoxide **1** was prepared by monoepoxidation of COT in accordance with a previously described procedure.[24]

Reactions were monitored by thin-layer chromatography (TLC) with Alugram SIL G/UV254 silica-gel sheets with detection by 0.5% phosphomolybdic acid solution in 95% EtOH or ethanolic *p*-anisaldehyde containing acetic acid and H_2SO_4. Silica gel 60 (230−400 mesh) was used for flash chromatography. Solvents for extraction and chromatography were of HPLC grade.

^1H NMR spectra were recorded at 200 MHz in $CDCl_3$ solution unless otherwise specified. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: $\delta = 7.26$ ppm). ^{13}C NMR spectra were recorded at 50 MHz with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: $\delta = 77.7$ ppm). The relative stereochemistry of bicyclic compounds **5a−g** and **6a−g** was established from ROESY spectra, which were recorded at 600 MHz with a mixing time of 0.6 s. The spectral width used was the minimum required in both dimensions. The pulse delay was maintained at 6 s; 200 increments of 4 scans and 2 K data points each were collected.

Analytical high-performance liquid chromatography (HPLC) was performed on a Daicel Chiralcel OB-H column with a 0.5 mL solvent flow and detection at 225 nm. For other general information, see references 11 and 15.

Reference racemic compounds **4a−c** were prepared by CuCN-promoted addition of Grignard reagents to COT monoepoxide **1**[11] as follows. A stirred suspension of CuCN (1.504 g, 16.78 mmol) in anhydrous THF (35 mL) was slowly added to RMgX (13.98 mmol) at −18 °C. After 20 min, a solution of freshly distilled **1** (560 mg, 4.66 mmol) in THF (3 mL) was added and the resulting solution was allowed to warm to 0 °C. The mixture was quenched (1−3 h) at 0 °C with a saturated aqueous NH_4Cl solution (reaction followed by TLC) and the aqueous layer was extracted with Et_2O. Evaporation of the dried ($MgSO_4$) organic phase afforded a crude product which was directly used in the next step. BuMgCl: 99% crude yield; EtMgBr: 99% crude yield; MeMgBr: 95% crude yield. For spectroscopic data of compounds **4a−c**, see reference 11.

Highly Enantioselective Synthesis of Compounds 4a−c by Copper/(*R*,*R*,*R*)-3-catalyzed Addition of R_2Zn to 1. General Procedure: A solution of $Cu(OTf)_2$ (54 mg, 0.15 mmol) and chiral ligand (*R*,*R*,*R*)-**3** (161 mg, 0.3 mmmol) in anhydrous toluene (6 mL) was stirred at room temp. for 40 min. The colorless solution was cooled to −78 °C followed by subsequent addition of a solution of **1** (1.20 g, 10.0 mmol) in toluene (2 mL). After 5 min, R_2Zn (15.0 mmol, 1.5 equiv.) was added and the stirred reaction mixture was allowed to warm slowly to 0 °C. After complete conversion, the mixture was quenched (3−6 h) at 0 °C with saturated aqueous NH_4Cl solution (5 mL). Extraction with Et_2O (2 × 35 mL) and evaporation of the dried ($MgSO_4$) organic phase afforded a crude product containing cyclooctatrienols **4a−c** and chiral ligand **3** which was directly used in the next step. Et_2Zn: 91% crude yield (93% *ee*); Me_2Zn: 81% crude yield (94% *ee*); Bu_2Zn: 95% crude yield (96% *ee*).

Attempted purification of compounds **4a−c** by distillation gave substantial conversion into the corresponding 4-alkyl-2,6-cyclooctadienones **7a−c** (vide infra). Compounds **4a−c** can be obtained with high purity, albeit with partial decomposition, by flash chromatography (SiO_2, 85:15 hexanes/EtOAc + 1% NEt_3). For spectroscopic data of compounds **4a−c** see reference 11.

General Procedure for Protocol A: A solution of optically active cyclooctatrienols **4a−c** (1.33 mmol) in anhydrous pyridine (4.0 mL) was treated at 0 °C in the presence of dimethylaminopyridine (DMAP; 10 mg) and R^1COCl (2.66 mmol, 2.0 equiv.). After 18 h at room temp., the reaction was quenched with H_2O and extracted with Et_2O. Evaporation of the washed organic solution (saturated aqueous $CuSO_4$, brine) afforded a crude reaction mixture that was filtered through SiO_2 (using hexanes containing 4% of EtOAc as the eluent).

General Procedure for Protocol B:[25] A solution of optically active cyclooctatrienols **4a−c** (1.12 mmol) in CH_2Cl_2 (10 mL) was treated with R^1COOH (1.34 mmol, 1.2 equiv.), stirred for 5 min, and then dicyclohexylcarbodiimide (DCC; 278 mg, 1.34 mmol) and DMAP (16 mg, 0.13 mmol) were added. After 18 h at room temp. the reaction mixture was filtered and the filtrate was evaporated. The residue was taken up in CH_2Cl_2 and again filtered. The CH_2Cl_2 solution was washed (0.5 N HCl and saturated aqueous $NaHCO_3$ solution) and concentrated followed by filtration through a short SiO_2 column eluting with CH_2Cl_2.

Reaction of 4a with *p*-Nitrobenzoyl Chloride (Protocol A): Following the general procedure a solution of optically active ethylcyclooctatrienol **4a** (250 mg, 1.86 mmol) in anhydrous pyridine (5.0 mL) in the presence of dimethylaminopyridine was treated at 0 °C with *p*-nitrobenzoyl chloride (640 mg, 3.72 mmol). The usual workup

afforded a crude reaction mixture that was purified by flash chromatography eluting with hexanes containing 5% of Et_2O to give 190 mg (36% yield) of an approximate 8:2 mixture of **5a** and **6a**, respectively. Further chromatographic purification on semipreparative TLC (hexanes containing 5% of Et_2O) gave, as the first eluting fraction 15 mg of pure (1*R*,6*S*,7*R*,8*S*)-8-methyl-7-(*p*-nitrobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**6a**) as a solid. M.p. 68−69 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.08−8.41 (m, 4 H), 5.66−5.71 (m, 3 H), 5.56−5.68 (m, 1 H), 5.04 (t, J = 6.6 Hz, 1 H), 2.84−3.28 (m, 3 H), 1.27 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.7, 131.4, 126.6, 125.1 (2C), 124.9 (2C), 124.2, 123.6, 84.0, 47.8, 39.5, 31.6, 13.9 ppm. $C_{16}H_{15}NO_4$: calcd. C 67.36, N 4.91, H 5.30; found C 67.57, N 4.66, H 5.40.

The second eluting fraction gave pure (1*S*,6*R*,7*R*,8*S*)-8-methyl-7-(*p*-nitrobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**5a**) as a solid. M.p. 76−77 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.08−8.28 (m, 4 H), 5.86−6.01 (m, 1 H), 5.66−5.78 (m, 2 H), 5.49 (dd, J = 4.1, 10.1 Hz, 1 H), 5.16 (t, J = 7.8 Hz 1 H), 3.61−3.76 (m, 1 H), 3.01−3.11 (m, 1 H), 2.31−2.41 (m, 1 H), 1.22 (d, J = 6.85 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 136.2, 131.5, 126.5, 125.6, 124.2 (2C), 123.8, 122.7, 82.9, 47.5, 39.0, 34.5, 18.5 ppm. $C_{16}H_{15}NO_4$: calcd. C 67.36, N 4.91, H 5.30; found C 67.77, N 4.86, H 5.35.

Reaction of 4b with *p*-Nitrobenzoic Acid (Protocol B): Following the general procedure a solution of optically active cyclooctatrienol **4b** (150 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was treated with DCC (249 mg, 1.2 mmol), *p*-nitrobenzoic acid (201 mg, 1.2 mmol) and DMAP (15 mg, 0.12 mmol). After 18 h at room temp., usual workup and chromatographic purification afforded 247 mg (83% yield) of an approximate 7:3 mixture of **5b/6b**. A 100-mg sample was further purified by semipreparative TLC eluting with 5% Et_2O in hexanes to afford, as the first eluting fraction, pure (1*R*,6*S*,7*R*,8*S*)-8-ethyl-7-(*p*-nitrobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**6b**; 7 mg) as a solid. M.p 73−75 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.17−8.31 (m, 4 H), 5.74−5.94 (m, 4 H), 5.10 (t, J = 7.3 Hz, 1 H), 3.22−3.27 (m, 1 H), 2.86−3.10 (m, 2 H), 1.63−1.78 (m, 2 H), 0.93 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, C_6D_6: δ = 163.4, 130.1, 128.8, 127.5, 125.2, 124.6, 124.4, 123.0, 122.8, 81.9, 54.0, 39.0, 30.3, 21.4, 11.9 ppm. $C_{17}H_{17}NO_4$: calcd. C 68.21, N 4.68, H 8.98; found C 68.65, N 4.58, H 8.91.

The second eluting fraction gave pure (1*S*,6*R*,7*R*,8*S*)-8-ethyl-7-(*p*-nitrobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**5b**; 35 mg), as a light-yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.17−8.32 (m, 4 H), 5.89−5.93 (m, 1 H), 5.71−5.74 (m, 2 H), 5.46 (dd, J = 9.8, 3.7 Hz, 1 H), 5.21 (t, J = 7.3 Hz, 1 H), 3.61−3.64 (m, 1 H), 2.90−3.03 (m, 1 H), 2.30−2.40 (m, 1 H), 1.40−1.86 (m, 2 H), 0.92 (t, J = 7.4 Hz 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.7, 136.2, 131.5 (2C), 127.2, 125.6, 124.2, 123.7, 122.5, 81.2, 54.3, 38.9, 33.1, 27.1, 12.6 ppm. $C_{17}H_{17}NO_4$: calcd. C 68.21, N 4.68, H 8.98; found C 68.87, N 4.60, H 8.95.

Reaction of 4c with *p*-Nitrobenzoic Acid (Protocol B): Following the general procedure, a solution of optically active cyclooctatrienol **4c** (450 mg, 2.7 mmol) in CH_2Cl_2 (27 mL) was treated with DCC (672.3 mg, 3.24 mmol), *p*-nitrobenzoic acid (543 mg, 3.24 mmol) and DMAP (41 mg, 0.32 mmol). After 18 h at room temp., usual workup and chromatographic purification afforded 706 mg (80% yield) of a mixture of **5c/6c**. A 110-mg sample was further purified by semipreparative TLC eluting with 5% Et_2O in hexanes to give, as the first eluting fraction, pure (1*R*,6*S*,7*R*,8*S*)-8-butyl-7-(*p*-nitrobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**6c**; 8 mg) as a solid. M.p. 71−72 °C. ^{1}H NMR (200 MHz, C_6D_6: δ = 7.64−7.80 (m, 4 H), 5.75−5.96 (m, 3 H), 5.42−5.53 (m, 1 H), 5.21 (t, J = 7.3 Hz, 1 H), 2.66−3.03 (m, 3 H), 1.47−1.71 (m, 2 H), 1.13−1.37 (m, 4 H), 0.87 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, C_6D_6: δ = 163.5, 130.5, 128.3, 127.8, 125.7, 125.0, 124.8, 123.4, 123.1, 82.3, 52.6, 39.5, 30.8, 30.3, 28.4, 23.0, 14.2 ppm. $C_{19}H_{21}NO_4$: calcd. C 69.71, N 4.28, H 6.47; found C 69.80, N 4.25, H 6.41.

The second eluting fraction gave pure (1*S*,6*R*,7*R*,8*S*)-8-butyl-7-(*p*-nitrobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**5c**; 29 mg), as a light-yellow oil. ^{1}H NMR (200 MHz, C_6D_6): δ = 7.61−7.85 (m, 4 H), 5.77−5.90 (m, 1 H), 5.45−5.70 (m, 3 H), 5.08 (t, J = 7.7 Hz, 1 H), 3.43−3.57 (m, 1 H), 3.04 (quint, J = 7.8 Hz, 1 H), 2.00 (ddd, 1 H, J = 9.6, 9.4, 5.5 Hz), 1.05−1.56 (m, 6 H), 0.85 (t, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 163.7, 135.3, 130.6, 128.8, 127.8, 126.6, 125.2, 123.5, 122.1, 81.1, 52.3, 38.7, 33.5, 33.0, 30.0, 22.9, 14.1 ppm. $C_{19}H_{21}NO_4$: calcd. C 69.71, N 4.28, H 6.47; found C 69.88, N 4.35, H 6.31.

Reaction of 4b with *p*-Bromobenzoyl Chloride (Protocol A): Following the general procedure, a solution of ethylcyclooctatrienol **4b** (150 mg, 0.84 mmol) in anhydrous pyridine (4.0 mL) in the presence DMAP (10 mg) was treated at 0 °C with *p*-bromobenzoyl chloride (369 mg, 1.68 mmol). The usual workup afforded a crude reaction mixture (340 mg) that was purified by flash chromatography eluting with hexanes containing 5% of Et_2O to give 116 mg (42% yield) of an approximate 8:2 mixture of **5d** and **6d**, respectively. Further chromatographic purification by semipreparative TLC gave, as the first eluting fraction, 10 mg of pure (1*R*,6*S*,7*R*,8*S*)-8-ethyl-7-(*p*-bromobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**6d**) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.79−7.92 (m, 2 H), 7.44−7.56 (m, 2 H), 5.79−5.90 (m, 1 H), 5.69−5.78 (m, 2 H), 5.51−5.64 (m, 1 H), 4.99 (t, J = 7.6 Hz, 1 H), 3.06−3.21 (m, 1 H), 2.87−2.95 (m, 1 H), 2.79−2.86 (m, 1 H), 1.53−1.72 (m, 2 H), 0.85 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.8, 132.5, 131.9, 129.9, 128.7, 126.3, 125.5, 125.0, 122.4, 82.1, 54.7, 43.4, 31.0, 26.2, 13.0 ppm. $C_{17}H_{17}BrO_2$: calcd. C 60.91, H 5.71; found C 61.30, H 5.40.

The second eluting fractions afforded 50 mg of pure (1*S*,6*R*,7*R*,8*S*)-8-ethyl-7-(*p*-bromobenzoyloxy)bicyclo[4.2.0]octa-2,4-diene (**5d**), also as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.79−7.90 (m, 2 H), 7.47−7.56 (m, 2 H), 5.77−5.89 (m, 1 H), 5.61−5.69 (m, 2 H), 5.40 (dd, J = 9.9, 3.8 Hz, 1 H), 5.10 (t, J = 7.8 Hz, 1 H), 3.47−3.62 (m, 1 H), 2.79−2.99 (m, 1 H), 2.31 (ddd, J = 9.7, 4.9, 1.9 Hz, 1 H), 1.35−1.65 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.3, 132.5, 131.9, 129.8, 128.8, 127.2, 125.4, 124.2, 122.5, 80.8, 54.4, 39.0, 33.1, 27.2, 12.7 ppm. $C_{17}H_{17}BrO_2$: calcd. C 60.91, H 5.71; found C 61.12, H 5.33.

(1*S*,6*R*,7*R*,8*S*)-8-Ethyl-7-(pentanoyloxy)bicyclo[4.2.0]octa-2,4-diene (5e) and (1*R*,6*S*,7*R*,8*S*)-8-Ethyl-7-(pentanoyloxy)bicyclo[4.2.0]octa-2,4-diene (6e): Following the general procedure (Protocol B), a solution of cyclooctatrienol **4b** (100 mg, 0.56 mmol) in CH_2Cl_2 (6 mL) was treated with DCC (162.3 mg, 0.80 mmol), pentanoic acid (0.087 mL, 0.80 mmol) and DMAP (10.0 mg, 0.08 mmol). After 18 h at room temp. usual workup and chromatographic purification afforded 118 mg (90% yield) of an approximate 85:15 inseparable mixture of **5e** and **6e**.

5e: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.78−5.93 (m, 1 H), 5.60−5.75 (m, 2 H), 5.40 (dd, J = 9.7, 3.7 Hz, 1 H), 4.92 (t, J = 7.8 Hz, 1 H), 3.41−3.56 (m, 1 H), 2.67−2.88 (m, 1 H), 2.20−2.48 (m, 3 H), 1.23−1.71 (m, 6 H), 0.78−0.96 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.4, 127.1, 125.2, 124.4, 122.4, 80.0, 54.2, 38.8, 35.7, 34.6, 33.0, 27.8, 27.2, 23.0, 14.4 ppm.

6e: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.63−5.95 (m, 3 H), 5.56 (dd, J = 9.9, 3.8 Hz, 1 H), 4.82 (t, J = 7.5 Hz, 1 H) 3.03−3.18 (m, 1 H), 2.67−2.88 (m, 2 H), 2.18−2.48 (m, 3 H), 1.23−1.72 (m, 6

H), 0.80−0.95 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.3, 126.3, 125.6, 124.9, 122.7, 81.1, 54.7, 39.6, 34.7, 30.9, 27.0, 22.7, 22.2, 14.9, 12.6 ppm.

(1*S*,6*R*,7*R*,8*S*)-8-Butyl-7-(pentanoyloxy)bicyclo[4.2.0]octa-2,4-diene (5f) and (1*R*,6*S*,7*R*,8*S*)-8-Butyl-7-(pentanoyloxy)bicyclo[4.2.0]octa-2,4-diene (6f): Following the general procedure (Protocol B), a solution of compound **4c** (200 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) was treated with DCC (278 mg, 1.34 mmol), pentanoic acid (0.145 mL, 1.34 mmol) and DMAP (16 mg, 0.13 mmol). After 18 h at room temp. the reaction mixture was filtered and the filtrate evaporated. The residue was taken up in CH_2Cl_2 and again filtered. The CH_2Cl_2 solution was washed (0.5 N HCl and saturated aqueous $NaHCO_3$ solution) and concentrated. Filtration through a short SiO_2 column eluting with CH_2Cl_2 afforded 230 mg (88% yield) of an inseparable 86:14 mixture of compounds **5f** and **6f**, respectively.
5f: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.83−5.96 (m, 1 H), 5.65−5.72 (m, 2 H), 5.40 (dd, J = 9.7, 3.8 Hz, 1 H), 4.93 (t, J = 7.7 Hz, 1 H), 3.43−3.56 (m, 1 H), 2.72−2.96 (m, 1 H), 2.20−2.51 (m, 3 H), 1.13−1.73 (m, 10 H), 0.80−0.98 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.2, 126.8, 125.0, 124.3, 122.3, 80.2, 52.3, 38.8, 35.5, 34.4, 34.0, 33.2, 27.7, 26.8, 22.9, 22.6, 14.2 ppm.
6f: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.65−5.96 (m, 3 H), 5.53−5-63 (m, 1 H), 4.83 (t, J = 7.0 Hz, 1 H), 3.02−3.18 (m, 1 H), 2.72−2.96 (m, 2 H), 2.20−2.37 (m, 2 H), 1.20−1.73 (m, 10 H), 0.81−0.97 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.1, 126.3, 125.5, 124.8, 122.8, 81.1, 52.8, 39.7, 38.8, 34.7, 33.9, 31.3, 31.0, 30.4, 23.2, 19.7, 14.6 ppm.

(1*S*,6*R*,7*R*,8*S*,2′*E*,4′*Z*)-8-Ethyl-7-(hexa-2′,4′-dienoyloxy)bicyclo-[4.2.0]octa-2,4-diene (5g) and (1*R*,6*S*,7*R*,8*S*,2′*E*,4′*Z*)-8-Ethyl-7-(hexa-2′,4′-dienoyloxy)bicyclo[4.2.0]octa-2,4-diene (6g): Following the general procedure (Protocol B), a solution of optically active cyclooctatrienol **4b** (250 mg, 1.67 mmol) in CH_2Cl_2 (15 mL) was treated with DCC (413.5 mg, 2.0 mmol), 2,4-hexadienoic acid (224 mg, 2.0 mmol) and DMAP (25 mg, 0.20 mmol). After 18 h at room temp. usual workup and chromatographic purification afforded 275 mg (65% yield) of an approximate 80:20 inseparable mixture of **5g** and **6g**.
5g: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.03−7.32 (m, 2 H), 6.04−6.23 (m, 2 H), 5.55−5.89 (m, 3 H), 5.36 (dd, J = 9.8, 3.8 Hz, 1 H), 4.93 (t, J = 7.7 Hz, 1 H), 3.38−3.52 (m, 1 H), 2.66−2.86 (m, 1 H), 2.14−2.29 (m, 1 H), 1.77 (d, J = 5.2 Hz, 3 H), 1.30−1.64 (m, 2 H), 0.78 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.7, 146.0, 140.2, 130.4, 127.1, 125.1, 124.6, 122.4, 119.3, 80.0, 54.2, 39.0, 33.0, 27.2, 19.4, 12.7 ppm.
6g: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20−7.33 (m, 2 H), 5.95−6.22 (m, 2 H), 5.58−5.86 (m, 3 H), 5.51 (dd, J = 9.5, 3.6 Hz, 1 H), 4.83 (t, J = 7.2 Hz, 1 H), 2.98−3.13 (m, 1 H), 2.65−2.87 (m, 2 H), 1.78 (d, J = 5.2 Hz, 3 H), 1.30−1.64 (m, 2 H), 0.80 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.2, 145.8, 126.3, 126.0, 125.7, 124.2, 123.1, 122.8, 119.5, 81.1, 54.8, 43.5, 39.6, 30.9, 22.2, 12.9 ppm.

Typical Procedure for the Synthesis of Enantio-Enriched 4-Alkyl-2,6-cyclooctadienones

(4*R*)-4-Ethyl-2,6-cyclooctadiene-1-one (7b): A solution of compound **4b** (1.0 g, 6.66 mmol) in toluene (3 mL) was heated at reflux for 1 h. Evaporation of the solvent followed by a short-path distillation (120 °C, 4 Torr) afforded pure **7b** (0.850 g, 85% yield) as a colorless liquid that became yellow on standing. $[\alpha]_D^{20}$ = +262.5 (c = 1.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.03−6.17 (m, 1 H), 5.95 (d, J = 12.3, 7.3 Hz, 1 H), 5.44−5.66 (m, 2 H), 3.72−3.86 (m, 1 H), 3.09−3.20 (m, 1 H), 2.91−3.01 (m, 1 H), 2.40−2.53 (m, 1 H), 1.85−2.04 (m, 1 H), 1.03−1.56 (m, 2 H), 0.78 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.8, 148.6, 131.7, 130.7, 121.4, 44.7, 39.7, 34.6, 30.6, 13.0 ppm. MS (EI, 70 eV): m/z (%)= 150 (6) [M^+], 106 (15), 96 (59), 67 (12), 53 (28), 39 (28). $C_{10}H_{14}O$: calcd. C 79.96, H 9.39; found C 78.86, H 8.98. The enantiomeric excess (94%) was determined by chiral HPLC (OB-H) (hexanes/2-propanol: 99:1): t_R = 14.1 (major); t_R = 16.8 (minor).

(4*R*)-4-Methyl-2,6-cyclooctadiene-1-one (7a): A solution of compound **4a** (1.0 g, 7.3 mmol) in toluene (3 mL) was heated at reflux for 1 h. Evaporation of the solvent followed by a short-path distillation (115 °C, 4 Torr) afforded pure **7a** (0.694 g, 70% yield) as a light-yellow liquid. $[\alpha]_D^{20}$ = +298.4 (c = 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.04 (dd, J = 7.3, 5.5 Hz, 1 H), 5.82−5.89 (m, 1 H), 5.46−5.56 (m, 2 H), 3.64−3.75 (m, 1 H), 3.28−3.43 (m, 1 H), 2.86−2.98 (m, 1 H), 2.33−2.45 (m, 1 H), 1.93−2.03 (m, 1 H), 1.1 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.2, 149.7, 131.9, 130.1, 121.5, 44.8, 36.9, 32.8, 23.2 ppm. MS (EI, 70 eV): m/z (%)= 136 (10) [M^+], 82 (100), 81 (41), 92 (12), 54 (54), 39 (62). $C_9H_{12}O$: calcd. C 79.36, H 8.89; found C 78.96, H 8.96. The enantiomeric excess (93%) was determined by chiral HPLC (OB-H) (hexanes/2-propanol: 99:1): t_R = 16.2 (major); t_R = 24.7 (minor).

(4*R*)-4-Butyl-2,6-cyclooctadiene-1-one (7c): A solution of compound **4c** (0.90 g, 5.5 mmol) in toluene (3 mL) was heated at reflux for 1 h. Evaporation of the solvent followed by a short-path distillation (130 °C, 4 Torr) afforded pure **7c** (0.657 g, 73% yield) as a light-yellow liquid. $[\alpha]_D^{20}$ = +231.0 (c = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.07 (dd, J = 12.2, 7.2 Hz, 1 H), 5.94 (d, J = 12.2 Hz, 1 H), 5.43−5.66 (m, 2 H), 3.68−3.84 (m, 1 H), 3.12−3.31 (m, 1 H), 2.87−3.02 (m, 1 H), 2.36−2.53 (m, 1 H), 1.83−2.05 (m, 1 H), 1.19−1.52 (m, 6 H), 0.80−0.95 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.3, 149.3, 132.0, 130.9, 121.6, 45.1, 38.4, 37.9, 35.3, 30.3, 23.3, 14.7 ppm. MS (EI, 70 eV): m/z (%)= 178 (5) [M^+], 150 (18), 124 (41), 53 (47), 39 (37). $C_{12}H_{18}O$: calcd. C 80.84, H 10.18; found C 79.96, H 9.98. The enantiomeric excess (96%) was determined by chiral HPLC (OB-H) (hexanes/2-propanol: 97:3): t_R = 11.2 (major); t_R = 12.6 (minor).

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