# Face-Selective and *endo*-Selective Cycloadditions with Enantiomerically Pure Cyclopentadienes

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A general synthetic route to the enantiopure bicyclic cyclopentadienes (*S*)-**3** and (*R*)-**3** of the hydrindane series, starting from the Hajos-Wiechert ketone **4** or its enantiomer is described. Reasons for the excellent face and *endo* selectivity of cycloadditions and the resulting consequences for chiral recognition are discussed.

Encouraged by the high β-face and *endo* selectivity reported for the cycloadditions of the steroid-derived cyclopentadiene **1a** by Solo[1] and by Bull[2], we prepared the phenyl derivative **1b** with the intention to perform highly diastereoselective transformations with Diels-Alder adducts to this 4π system, in order to release at a later stage enantiopure building blocks in a thermal retro reaction. Additionally, we could easily predict chiral discrimination[18] resulting in kinetic resolution of racemic dienophiles having their stereogenic center in close neighborhood of the 2π system (see **10**).

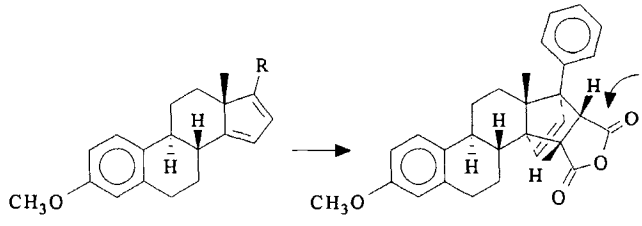
It was with these aims in mind that we replaced the *O*-acetate of the Solo-Bull diene by a phenyl ring or an aromatic system (see below), since a threefold task was assigned to this substituent.

First of all, to realize regioselectivity of Diels-Alder cycloadditions, it had to take the function of an inert donor substituent, similar to the acetoxy groups, but as hydride reductions as well as organometallic transformations were also planned to be performed with the later cycloadducts a carbonyl group was clearly undesirable. Second, this aromatic ring system was expected to shield functional groups in the cycloadducts to be formed, thus improving the chances for diastereoselective transformations at this stage. Finally, as a third function of the aromatic ring we hoped for a much lower activation barrier for the retro Diels-Alder process since Czarnik and his collaborators reported on a substantial enhancement of rates for retro reactions with phenyl-substituted cycloadducts[3–5], an observation which may find its explanation in recent results communicated by Hall and co-workers[6].

We have already reported on the synthesis of enantiopure **1b**[7]. All these expectations were satisfied with this diene and its cycloadducts and an additional observation was made with adducts formed from symmetric dienophiles like maleic anhydride, e.g. **2**.

Although the transformations with **2** proved of course to be highly diastereoselective we observed with these cyclic anhydrides also a quite interesting regioselectivity. Nucleophilic attack on this moiety took place preferentially at the carbonyl group neighboring the phenyl ring (see arrow!) which is located nearly perpendicular to the steroid ring system[7]. As an explanation for this result we assumed the C-7-sp$^3$ center of ring B to exercise a stronger influence on the carbonyl attack than the phenyl group at C-17.

Scheme 1




**1a** R= OAc **2**

**1b** R= $C_6H_5$

Since with anhydrides of this type regioselectivity in carbonyl transformations is translated directly into enantioselectivity, this observation called for further inspection.

The easiest way to check the explanation given above would certainly be the investigation of cycloadducts that are lacking both these rings altogether. This demanded the preparation of simple dienes of the general structure **3**, which were considered desirable also for a number of additional reasons.

First of all, the steroid-derived diene **1b** had only been our first choice in this field because it could easily be prepared in optical pure form from dehydroestrone in a simple reaction sequence[7,8]. We were well aware of the fact, however, that if these initial promising results led to more detailed investigations into template-directed transformations including chiral recognition experiments, then an inexpensive enantiopure source for a much more flexible synthesis of chiral cyclopentadienes would be mandatory.

Additionally, with steroids there is the unacceptable deficit in that actually only one enantiomer of the diene becomes available while the configurational flexibility desired

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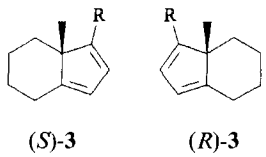
for the whole concept clearly called for the availability of both absolute configurations in the diene.

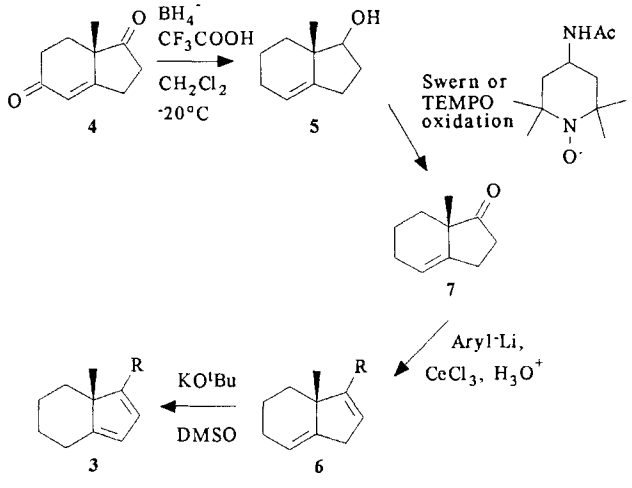
Scheme 2




| 3 | R |
|---|---|
| a | $C_6H_5$ |
| b | 4-$H_3COC_6H_4$ |
| c | 2-$H_3COC_6H_4$ |
| d | 2,4-$(H_3CO)_2C_6H_3$ |
| e | 2-naphthyl |

All these requirements are met with dienes of type **3**[7]. The starting material of choice would be the easily available Hajos-Wiechert ketone (*S*)- or (*R*)-**4** which is of course available in both absolute configurations, depending on the choice of the proline used as the catalyst for the preparation of the two ketones **4**. Since only 2-methyl-1,3-cyclopentanedione and methyl vinyl ketone are necessary for the preparation and as this diketone was prepared by the original authors as a potential starting material for an industrial steroid total synthesis, one can also obtain quite large amounts of these compounds.

Scheme 3




The reductive removal of the carbonyl group at C-5 can in principle be achieved in various ways in different yields[9]. With unsaturated ketones there arises in many cases the problem of double-bond migration[10], which in our case would have led to a useless compound. Therefore, in our first experiments[7] we returned to the thioketal reduction[11]. Although the yield was acceptable, the inconveniences encountered with a large-scale Birch process and the handling of the corresponding thio compounds were the main reasons to develop a variation of Gribble's method to reduce aromatic ketones completely[12].

Expecting similarities between an aromatic and an α,β-unsaturated ketone, we applied his procedure (borohydride reduction in trifluoroacetic acid at room temperature) to the Hajos-Wiechert ketone **4**, but with unsatisfactory results. Although the unsaturated alcohol **5** was formed, the yield was poor, a number of byproducts were formed and the whole process was unreliable and irreproducible. When the trifluoroacetic acid was diluted, however, with dichloromethane or a mixture of dichloromethane and acetonitrile and the borohydride was added in a temperature range between −10 and −15°C this procedure[13] provided reliably high yields of alcohol **5**. For the introduction of the aromatic substituent compound **5** had to be oxidized to the corresponding ketone **7**. PCC may be used for this oxidation but the yield never exceeded 60% and as we additionally wanted to remove the chromic acid reagent we also successfully employed the Swern process (90%). Very satisfactory results were also obtained with Bobbitt's[14] TEMPO reagent. In this case, however, it is advisable to purify the raw material by silica-gel filtration prior to distillation. A quite attractive aspect of this procedure is the fact that the corresponding hydroxylamine that results from the *N*-oxide radical precipitates from the solutions. As a consequence, workup just comprised filtration to recover the reduced form of the reagent, which may be reoxidized quite easily. Again, ketone **7** may be obtained in a reproducible yield of 85%.

This ketone was a very suitable intermediate for the preparation of all the desired dienes in this field, since at this stage the choice of the organometallic reagent for nucleophilic attack at the carbonyl group determines the structure of the diene to be prepared.

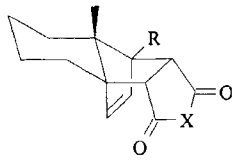
In general, the corresponding aryllithium compounds were used in this process but slightly higher yields could be achieved if these reagents were transmetalated by cerium trichloride to generate the nonenolizing cerium derivatives. The tertiary benzylic alcohols obtained in this way are of course very prone to elimination leading to the deconjugated diene **6** on acid treatment. The structures of these compounds were unambiguously derived from their NMR spectra and the typical styrene-type UV absorptions. Rearrangement to the cyclopentadiene isomer under acidic conditions occurred only to an insignificant extent. The crude reaction mixture of the elimination process was therefore treated without any further purification with a solution of potassium *tert*-butoxide in dimethyl sulfoxide to furnish the cyclopentadienes of type (*S*)-**3** in good yields. The preparation of the other enantiomer (*R*)-**3** followed of course the same lines and (*R*)-**3a** as well as (*R*)-**3b** were already synthesized in this way to be used in chiral discrimination experiments.

All the dienes were characterized as crystalline maleimide adducts **8**, which were easily obtained in nearly quantitative yields with complete face selectivity and exclusively with *endo* selectivity. The same holds for the corresponding anhydrides **9**, thus proving these dienes to be by no means inferior to the steroid derivatives as far as selectivity is concerned.

According to expectations nucleophilic attack on the anhydride moiety showed reversed regioselectivity[15] compared to **2** which nicely demonstrates the directing influence of ring B in the steroid series.

The decisive role of the electron density in the aromatic ring which is obviously communicated to the 4π system is clearly reflected in the rates of the cycloaddition reactions.

Scheme 4



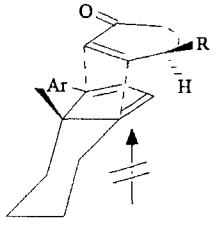

| | X |
|---|---|
| **8** | NH |
| **9** | O |

R: see **3**

While formation of the unsubstituted phenyl derivative **3a** requires heating in dichloromethane for 1–2 hours the corresponding *p*-methoxy compound is formed within a few hours at room temperature. A comparison of the addition rates in the electron-rich series **3b–d** including the β-naphthyl derivative **3e** revealed that only the *o*-methoxy compound **3c** adds to dienophiles at a somewhat slower rate than all the other cyclopentadienes. In contrast to the *p*-methoxy compound **3b** there is certainly some steric hindrance exerted by the *o*-substituent, which is probably electronically compensated in the *o,p*-dimethoxy derivative **3d**.

As far as face selectivity is concerned the concave-convex conformation of **3** may be held responsible for exclusive β-attack, since there are examples in the literature already, clearly indicating that conformational control in bicyclic molecules is superior to configurational control by methyl groups[16,17]. On the other hand, the angular methyl group very probably blocks the *exo* attack of the dienophiles.

Scheme 5




**10**

If this is taken for granted, one may safely predict efficient chiral discrimination by means of 2π systems like **10**, and for a number of cyclic dienophiles of this type perfect chiral discrimination has indeed been demonstrated already[18,19].

Continuous supply with starting materials from Dr. *H. Laurent*, Schering AG, Berlin, is gratefully acknowledged. We also thank the *DFG* (grant Wi 206/40-3) and the *Fonds der Chemischen Industrie* for financial support.

## Experimental

Melting points: Büchi melting point microscope. – UV: Beckman 3600; solutions in methanol. – IR: Perkin-Elmer 581. – $^1$H and $^{13}$C NMR: Bruker AM 200; internal standard tetramethylsilane. – MS: Finnigan MAT 312; 70 eV. – Elemental analyses: Heraeus CHN rapid analyzer. – Flash chromatography: Silica gel (300–600 mesh, Baker), 0.3 bar, all solvents were dried by the usual methods.

*General Procedure for the Preparation of the Dienes* **3a–e**: In a 4-l round-bottomed flask equipped with overhead stirrer, thermometer, cooled addition funnel, and Ar inlet 36.6 g (0.969 mol) of sodium borohydride was suspended in 750 ml of acetonitrile under Ar and the suspension was cooled to −15°C. To this suspension a solution of 40 g (0.242 mol) of **4** in 300 ml of dichloromethane was added dropwise at such a rate that the internal temperature never exceeded −12°C. Finally, 574 ml (855.3 g, 7.50 mol) of trifluoroacetic acid cooled to 0°C was slowly added dropwise to this mixture with stirring (again *the internal temperature of the flask must be kept between −10 and −15°C*). – After this addition, stirring was continued while the reaction mixture was slowly warmed to room temp. After 1 h at ambient temp., the mixture was carefully neutralized with dilute sodium hydroxide solution and by adding altogether 180 g of sodium hydroxide dissolved in water a basic suspension was obtained. After phase separation, the aqueous phase was extracted three times with 300 ml of dichloromethane, the combined organic phases were washed with 400 ml of 2 N NaOH to remove boric acid esters, then with 400 ml of brine, dried with magnesium sulfate and the solvent was evaporated under reduced pressure to afford 34.2 g (93%) of a slightly yellow solid material (**5**), which was sufficiently pure to be used immediately in the next step; m.p. 82°C (ether/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3294 cm$^{-1}$, 2929, 1337, 1068. – $^1$H NMR ($CDCl_3$, 90 MHz): δ = 5.36 (t, *J* = 1.1 Hz, 1H), 3.63 (dd, *J* = 10/8 Hz, 1H), 2.40–1.10 (m, 10H), 0.95 (s, 3H). – For the following oxidation two methods may be used.

a) *Swern Procedure:* 18 g (0.15 mol) of oxalic acid dichloride was dissolved in 50 ml of dichloromethane. At −70°C 23.4 g (0.3 mol) of dimethyl sulfoxide was added with stirring to the resulting solution. After 15 min at this temperature, a solution of 15.2 g (0.1 mol) of alcohol **5** in 20 ml of dichloromethane was added dropwise and the stirring was continued for another 40 min. Subsequently, 50.5 g (0.5 mol) of triethylamine was added dropwise to the mixture which was kept at −70°C for 45 min, then slowly warmed to room temp. After 15 min at ambient temp., the reaction mixture was poured into an excess of 20% aqueous citric acid and extracted three times with dichloromethane. The combined extracts were dried with magnesium sulfate, filtered and the solvent was evaporated from the filtrate under reduced pressure. The remaining oil was purified by kugelrohr distillation (50–60°C/0.4 Torr) to yield 13.8 g (92%) of ketone **7**.

b) *Bobbit Procedure:* 45.4 g (0.22 mol) of the TEMPO reagent[14] and 36.7 g (0.22 mol) of *p*-toluenesulfonic acid were dissolved in 350 ml of dichloromethane at −20°C and the obtained solution was stirred for 20 min. Then an ice-cold solution of 16.2 g (0.11 mol) of alcohol **5** in 35 ml of dichloromethane was added and the mixture was kept at room temp. until the red color had vanished and a white precipitate had formed. This precipitate was filtered for the recycling of the reagent and the clear solution was concentrated. The crude product was filtered through silica gel [ether/dichloromethane (1:1)] to yield 13.5 g (84%) of ketone **7**. – IR ($CHCl_3$): $\tilde{\nu}$ = 3018 cm$^{-1}$, 2940, 1732, 1452, 1264, 1136. – $^1$H NMR ($CDCl_3$, 90 MHz): δ = 5.36 (t, *J* = 1 Hz, 1H), 2.70–2.30 (m, 4H), 2.30–1.58 (m, 6H), 1.13 (s, 3H).

For the introduction of the various aryl substituents 35.7 g (95.8 mmol) of carefully dried cerium trichloride was added to 235 ml of dry THF in an inert gas. After stirring at room temp. for 2 h, the mixture was cooled to −78°C and 95.8 mmol of the corresponding aryllithium reagent was added. After 1–2 h at −78°C, a solution of 9.6 g (64 mmol) of ketone **7** in 15 ml of dry THF was added dropwise to the reaction mixture, which was kept for 1 h at −78°C. Then the mixture was quenched with an excess of a saturated ammonium chloride solution. The product was extracted several times with ether, the combined extracts were dried and the solvent was

evaporated under reduced pressure. The remaining raw material was filtered through silica gel (petroleum ether) to provide 97% of a colorless oil, the homogeneity of which was secured by HPLC and TLC in all cases. – These alcohols (26 mmol) were immediately dissolved in 300 ml of dichloromethane and, after addition of 300 mg (1.5 mmol) of *p*-toluenesulfonic acid, the clear solution was refluxed for 2 h, subsequently washed with a saturated sodium hydrogen carbonate solution and brine and finally concentrated. The residue was redissolved in a mixture of 75 ml of dry THF and 75 ml of dry dimethyl sulfoxide, then potassium *tert*-butoxide was added (28 mmol) and the colored solution was stirred at room temp. for 4 h. The reaction mixture was then poured into 150 ml of an aqueous ammonium chloride solution and the colorless product extracted three times with a total amount of 200 ml of ether. The ether solution was dried with magnesium sulfate and the solvent was evaporated under reduced pressure. The remaining oil was purified by flash chromatography with petroleum ether to yield 68–70% of the corresponding diene.

*(1S)-1-Methyl-9-phenylbicyclo[4.3.0]nona-6,8-diene* (**3a**): $[\alpha]_D$ = +82.3 (*c* = 1.00, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 205 nm, 218, 305. – IR ($CHCl_3$): $\tilde{\nu}$ = 3060 $cm^{-1}$, 2940, 2860, 1595, 1530, 1490, 1440, 840, 830, 690. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.12–7.56 (m, 5H), 6.73 (d, *J* = 2 Hz, 1H), 6.02 (d, *J* = 2 Hz, 1H), 2.63 (br. d, *J* = 13 Hz, 1H), 2.42 (br. d, *J* = 13 Hz, 1H), 2.27 (tdd, *J* = 13/5/2 Hz, 1H), 1.88–2.05 (m, 1H), 1.48–1.72 (m, 3H), 1.02–1.29 (m, 1H), 1.19 (s, 3H). – MS (20°C); *m/z* (%): 211 (20), 210 (100) [$M^+$], 195 (53), 182 (26), 181 (49), 180 (40), 179 (34), 178 (30), 167 (75), 165 (74), 152 (31). – $C_{16}H_{18}$ (210.32): calcd. 210.140851; found 210.1408193.

*(1S)-9-(4-Methoxyphenyl)-1-methylbicyclo[4.3.0]nona-6,8-diene* (**3b**): M.p. 46–48°C. – $[\alpha]_D$ = +276 (*c* = 0.55, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 202 nm, 225, 307. – IR (KBr): $\tilde{\nu}$ = 3047 $cm^{-1}$, 2932, 1605, 1574, 1506, 1264, 827. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.46 (d, *J* = 9 Hz, 2H), 6.86 (d, *J* = 9 Hz, 2H), 6.60 (d, *J* = 2 Hz, 1H), 5.99 (t, *J* = 2 Hz, 1H), 3.82 (s, 3H), 2.62 (d, *J* = 13 Hz, 1H), 2.26 (tdd, *J* = 13/4/2 Hz, 1H), 1.89 (m, 1H), 1.60 (m, 1H), 1.1 (m, 1H), 1.17 (s, 3H). – MS (20°C); *m/z* (%): 240 (100) [$M^+$], 225 (20), 212 (10), 211 (10), 197 (12), 165 (5), 153 (5), 121 (5). – $C_{17}H_{20}O$ (240.35): calcd. C 84.95, H 8.39; found C 84.71, H 8.33.

*(1S)-9-(2-Methoxyphenyl)-1-methylbicyclo[4.3.0]nona-6,8-diene* (**3c**): M.p. 49°C. – $[\alpha]_D$ = +202 (*c* = 0.55, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 215 nm, 282, 313. – IR (KBr): $\tilde{\nu}$ = 3056 $cm^{-1}$, 2936, 1618, 1592, 1573, 1490, 1248, 1026, 836, 753. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.16–7.34 (m, 2H), 6.88–7.00 (m, 2H), 6.70 (d, *J* = 2 Hz, 1H), 6.03 (t, *J* = 2 Hz, 1H), 3.81 (s, 3H), 2.64 (d, *J* = 12 Hz, 1H), 2.24 (tdd, *J* = 12/2/5 Hz, 1H), 2.11–2.24 (m, 1H), 1.87–2.03 (m, 1H), 1.49–1.66 (m, 2H), 1.03–1.28 (m, 2H), 1.09 (s, 3H). – MS (20°C); *m/z* (%): 240 (100) [$M^+$], 225 (31), 212 (9), 211 (16), 197 (24), 183 (10), 182 (7), 181 (14), 178 (9), 165 (18), 153 (7), 121 (9). – $C_{17}H_{20}O$ (240.35): calcd. C 84.95, H 8.39; found C 84.81, H 8.27.

*(1S)-9-(2,4-Dimethoxyphenyl)-1-methylbicyclo[4.3.0]nona-6,8-diene* (**3d**): M.p. 45°C. – $[\alpha]_D$ = +171.5 (*c* = 0.86, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 219 nm, 283, 305. – IR (KBr): $\tilde{\nu}$ = 3000 $cm^{-1}$, 2936, 2856, 1604, 1576, 1500, 1464, 1300, 1160, 1132. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.20 (d, *J* = 9 Hz, 1H), 6.64 (d, *J* = 2 Hz, 1H), 6.44–6.52 (m, 2H), 6.01 (t, *J* = 2 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.63 (dt, *J* = 1/3 Hz, 1H), 2.10–2.34 (m, 2H), 1.87–2.01 (m, 1H), 1.49–1.65 (m, 2H), 1.10–1.27 (m, 2H), 1.07 (s, 3H). – MS (20°C); *m/z* (%): 270 (100) [$M^+$], 256 (21), 242 (8), 228 (8), 151 (10), 91 (7). – $C_{18}H_{22}O_2$ (270.37): calcd. C 79.96, H 8.20; found C 79.24, H 8.22.

*(1S)-1-Methyl-7-(2-naphthyl)bicyclo[4.3.0]nona-6,8-diene* (**3e**): M.p. 80°C. – $[\alpha]_D$ = +267 (*c* = 0.52, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 223 nm, 274, 283, 324. – IR (KBr): $\tilde{\nu}$ = 3050 $cm^{-1}$, 2932, 1626, 1611, 1596, 862, 834, 810. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.67–7.88 (m, 4H), 7.34–7.50 (m, 3H), 6.89 (d, *J* = 2 Hz, 1H), 6.07 (m, 1H), 2.48–2.73 (m, 2H), 2.23–2.43 (m, 1H), 1.83–2.10 (m, 1H), 1.60–1.77 (m, 2H), 1.07–1.35 (m, 2H), 1.28 (s, 3H). – MS (20°C); *m/z* (%): 260 (100) [$M^+$], 245 (15), 232 (11), 215 (22), 203 (9), 202 (17), 165 (86). – $C_{20}H_{20}$ (260.38): calcd. C 92.26, H 7.74; found C 92.44, H 7.69.

*Imide Adducts* **8a–e**. – *General Procedure:* 0.5 mmol of the respective diene and 0.49 g (0.5 mmol) of maleimide were dissolved in 1 ml of dichloromethane and the resulting solution was stirred for 5 h. The solvent was evaporated under reduced pressure and the residue was filtered through silica gel [petroleum ether/ether (1:3)].

**8a**: Yield 128 mg (83%), m.p. 259°C. – $[\alpha]_D$ = –178.3 (*c* = 0.97, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3400 $cm^{-1}$, 3060, 2932, 1768, 1720, 1344, 1172. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 8.15 (m, 1H), 7.39–7.21 (m, 5H), 6.19 8d, *J* = 6 Hz, 1H), 6.13 (d, *J* = 6 Hz, 1H), 4.09 (d, *J* = 7 Hz, 1H), 3.16 (d, *J* = 7 Hz, 1H), 2.28 (m, 1H), 1.97 (ddd, *J* = 17/13/4 Hz, 1H), 1.75–1.03 (m, 5H), 0.78 (s, 3H), 0.71 (d, *J* = 13 Hz, 1H). – MS (130°C); *m/z* (%): 307 (100) [$M^+$], 292 (18), 221 (17), 212 (15), 210 (37), 195 (12), 194 (12), 181 (12), 178 (11), 167 (25), 165 (18), 95 (13), 92 (15), 91 (30), 73 (13). – $C_{20}H_{21}NO_2$ (307.39): calcd. 307.15718, found 307.15713 (MS). – calcd. C 78.15, N 4.56; found C 78.05, H 6.97, N 4.98.

**8b**: Yield 147 mg (86%), m.p. 207°C. – $[\alpha]_D$ = –102.5 (*c* = 0.55, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 2927 $cm^{-1}$, 2856, 1759, 1702, 1615, 1518, 1356, 1255, 1184. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.60 (m, 1H), 7.30 (dt, *J* = 9/2 Hz, 2H), 6.91 (dt, *J* = 9/2 Hz, 2H), 6.18 (d, *J* = 6 Hz, 1H), 6.13 (d, *J* = 6 Hz, 1H), 4.05 (d, *J* = 8 Hz, 1H), 3.82 (s, 3H), 3.17 (d, *J* = 8 Hz, 1H), 2.28 (d, *J* = 12 Hz, 1H), 1.87–2.03 (m, 1H), 1.13–1.76 (m, 5H), 0.78 (s, 3H), 0.72 (d, *J* = 13 Hz, 1H). – MS (20°C); *m/z* (%): 337 (17) [$M^+$], 322 (17), 251 (10), 242 (10), 241 (19), 240 (100), 225 (12), 211 (10), 197 (15), 165 (13), 115 (10), 91 (11), 84 (18), 61 (20), 49 (21). – $C_{21}H_{23}NO_3$ (337.42): calcd. 337.167794; found 337.168823 (MS).

**8c**: Yield 108 mg (64%), m.p. 200°C (decomp.). – $[\alpha]_D$ = –110.8 (*c* = 0.805, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3229 $cm^{-1}$, 2918, 2857, 1770, 1708, 1600, 1352, 1249, 1188, 1027. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.69 (m, 1H), 7.21–7.32 (m, 2H), 6.92–7.00 (m, 2H), 6.26 (d, *J* = 6 Hz, 1H), 5.99 (d, *J* = 6 Hz, 1H), 4.86 (d, *J* = 7 Hz, 1H), 3.81 (s, 3H), 3.11 (d, *J* = 7 Hz, 1H), 2.25 (d, *J* = 12 Hz, 1H), 1.86–2.07 (m, 1H), 1.12–1.76 (m, 5H), 0.84 (s, 3H), 0.64 (d, *J* = 13 Hz, 1H). – MS (120°C); *m/z* (%): 337 (33) [$M^+$], 279 (24), 278 (100), 254 (21), 251 (21), 240 (60), 197 (23), 165 (29), 115 (22), 91 (25), 57 (25), 55 (26). – $C_{21}H_{23}NO_3$ (337.42): calcd. 337.167794; found 337.167023.

**8d**: Yield 157 mg (86%), m.p. 92°C. – $[\alpha]_D$ = –18.1 (*c* = 1.00, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3244 $cm^{-1}$, 3068, 2924, 1768, 1708, 1612, 1508, 1464, 1208, 1192, 1144. – $^1H$ NMR ($CDCl_3$, 200 MHz): δ = 7.53 (m, 1H), 7.21 (d, *J* = 9 Hz, 1H), 6.47–6.54 (m, 2H), 6.23 (d, *J* = 6 Hz, 1H), 5.97 (d, *J* = 6 Hz, 1H), 4.75 (d, *J* = 7 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.09 (d, *J* = 7 Hz, 1H), 2.25 (d, *J* = 13 Hz, 1H), 1.88–2.05 (m, 1H), 1.12–1.76 (m, 5H), 0.82 (s, 3H), 0.65 (d, *J* = 13 Hz, 1H). – MS (250°C); *m/z* (%): 367 (17) [$M^+$], 352 (9), 307 (12), 271 (21), 270 (100), 255 (10), 227 (7), 165 (5), 91 (5), 91 (6), 57 (6), 55 (6). – $C_{22}H_{25}NO_4$ (367.44): calcd. 367.178359; found 367.178070.

**8e**: Yield 157 mg (86%), m.p. 242°C. – $[\alpha]_D$ = –236.2 (*c* = 0.99, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3188 $cm^{-1}$, 3056, 2924, 2856, 1768, 1708,

1344, 1192. – $^1$H NMR ($CHCl_3$, 200 MHz): δ = 7.80–7.91 (m, 4H), 7.71 (m, 1H), 7.42–7.54 (m, 3H), 6.31 (d, *J* = 6 Hz, 1H), 6.20 (d, *J* = 6 Hz, 1H), 4.23 (d, *J* = 7 Hz, 1H), 3.21 (d, *J* = 7 Hz, 1H), 2.31 (d, *J* = 13 Hz, 1H), 1.98–2.15 (m, 1H), 1.12–1.79 (m, 5H), 0.83 (s, 3H), 0.74 (d, *J* = 13 Hz, 1H). – MS (80°C); *m/z* (%) = 357 (8) [$M^+$], 260 (100), 246 (28), 232 (27), 231 (44), 230 (27), 229 (31), 228 (34), 219 (35), 217 (87), 216 (71), 204 (30), 203 (57), 191 (32), 165 (32), 123 (26), 115 (31), 109 (25). – $C_{24}H_{23}NO_2$ (357.45): calcd. 357.172879; found 357.172852.

*Anhydride Adducts* **9a–e**

**9a**: 105 mg (0.5 mmol) of diene (*S*)-**3a** and 53 mg (0.71 mmol) of maleic anhydride were dissolved in 5 ml of toluene and the mixture was heated for 4 h. After evaporation of the solvent and purification by flash-chromatography, 105 mg (68%) of white crystals was obtained. – M.p. 195°C. – $[\alpha]_D$ = –13.9 (*c* = 1.1, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 220 nm. – IR (KBr): $\tilde{\nu}$ = 2936 $cm^{-1}$, 2862, 1857, 1778, 1600, 1447, 1228, 1179, 1094, 922, 757, 693, 661. – $^1$H NMR ($CDCl_3$, 200 MHz): 7.22–7.47 (m, 5H), 6.28 (q, *J* = 6 Hz, 2H), 4.34 (d, *J* = 8 Hz, 1H), 3.43 (d, *J* = 8 Hz, 1H), 2.32 (br. d, *J* = 13 Hz, 1H), 1.96 (br. td, *J* = 13/4 Hz, 1H), 1.68–1.80 (m, 1H), 1.08–1.62 (m, 4H), 0.80 (s, 3H), 0.69–0.85 (m, 1H). – MS (90°C); *m/z* (%) = 308 (3) [$M^+$], 307 (13), 281 (11), 280 (46), 237 (14), 236 (72), 235 (18), 222 (19), 221 (100), 210 (23), 207 (22), 194 (42), 179 (39), 178 (43), 168 (34), 167 (68), 165 (58). – $C_{20}H_{20}O_3$ (308.38): calcd. C 77.89, H 6.54; found C 77.72, H 6.57.

**9b**: 116 mg (0.48 mmol) of diene (*S*)-**3b** and 65 mg (0.5 mmol) of maleic anhydride were dissolved in 1 ml of dichloromethane. After 20 min, the orange color of the solution faded away, the solvent was evaporated and the residue was filtered through silica gel to provide 117 mg (72%) of white crystals of m.p. 162°C. – $[\alpha]_D$ = –143 (*c* = 0.60, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 202 nm, 226. – IR (KBr): $\tilde{\nu}$ = 2922 $cm^{-1}$, 2863, 1855, 1776, 1613, 1517, 1257, 1181, 1093, 1025, 922. – $^1$H NMR ($CDCl_3$, 200 MHz): δ = 7.29 (d, *J* = 9 Hz, 2H), 6.93 (d, *J* = 9 Hz, 2H), 6.28 (d, *J* = 6 Hz, 1H), 6.24 (d, *J* = 6 Hz, 1H), 4.27 (d, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.41 (d, *J* = 7.5 Hz, 1H), 2.31 (d, *J* = 12 Hz, 1H), 1.94 (td, *J* = 13/4 Hz, 1H), 1.67–1.81 (m, 1H), 1.07–1.64 (m, 1H), 0.69–0.84 (m, 1H), 0.79 (s, 3H). – MS (150°C); *m/z* (%) = 338 (6) [$M^+$], 309 (6), 266 (14), 251 (18), 240 (100), 225 (10), 211 (8), 197 (16). – $C_{21}H_{22}O_4$ (338.40): calcd. C 74.54, H 6.55; found C 74.19, H 6.57.

**9c**: 2 g (8.75 mmol) of diene (*S*)-**3c** and 980 mg (10 mmol) of maleic anhydride were dissolved in 10 ml of dichloromethane and the obtained solution was sealed in a teflon tube which was pressurized at 6.5 kbar for 24 h. After evaporation of the solvent and crystallization of the residue from ether, 2.78 g (94%) of adduct **9c** was obtained. – M.p. 214°C. – $[\alpha]_D$ = –112 (*c* = 1.00, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 207 nm, 220. – IR (KBr): $\tilde{\nu}$ = 2927 $cm^{-1}$, 2860, 1854, 1774, 1599, 1495, 1463, 1253. – $^1$H NMR ($CDCl_3$, 200 MHz): δ = 7.19–7.37 (m, 2H), 6.91–7.04 (m, 2H), 6.35 (d, *J* = 6 Hz, 1H), 6.10 (d, *J* = 6 Hz, 1H), 5.22 (d, *J* = 8 Hz, 1H), 3.83 (s, 3H), 3.36 (d, *J* = 8 Hz, 1H), 2.28 (d, *J* = 12 Hz, 1H), 1.95 (td, *J* = 13/4 Hz, 1H), 1.63–1.80 (m, 1H), 1.07–1.63 (m, 4H), 0.86 (s, 3H), 0.68 (d, *J* = 13 Hz, 1H). – MS (150°C); *m/z* (%) = 338 (12) [$M^+$], 309 (36), 294 (5), 282 (12), 266 (46), 251 (57), 240 (100), 224 (20), 197 (32), 181 (21), 165 (24), 152 (12), 128 (12), 115 (16), 91 (25). – $C_{21}H_{22}O_4$ (338.4): calcd. C 74.54, H 6.55; found C 73.62, H 6.51.

**9d**: Preparation see **9b**, yield 147 mg (83%) starting from (*S*)-**3d**, m.p. 74°C. – $[\alpha]_D$ = –91.3 (*c* = 0.765, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 221 nm, 230, 283. – IR (KBr): $\tilde{\nu}$ = 2928 $cm^{-1}$, 2860, 1852, 1776, 1612, 1508, 1464, 1208, 1144, 1092, 1024, 916. – $^1$H NMR ($CDCl_3$, 200 MHz): δ = 7.16 (d, *J* = 9 Hz, 1H), 6.48–6.55 (m, 2H), 6.32 (d, *J* = 6 Hz, 1H), 6.08 (d, *J* = 6 Hz, 1H), 5.10 (d, *J* = 8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.33 (d, *J* = 8 Hz, 1H), 2.26 (d, *J* = 13 Hz, 1H), 1.83–2.01 (m, 1H), 1.27–1.77 (m, 5H), 0.83 (s, 3H), 0.67 (d, *J* = 13 Hz, 1H). – MS (120°C); *m/z* (%) = 368 (6) [$M^+$], 340 (5), 295 (8), 281 (12), 271 (20), 270 (100), 255 (11), 227 (9), 165 (6), 149 (8), 115 (6), 91 (6), 57 (11), 55 (11). – $C_{22}H_{24}O_5$ (368.43): calcd. C 71.72, H 6.57; found C 71.25, H 6.63.

**9e**: 204 mg (0.785 mmol) of diene (*S*)-**3e** was added to a solution of 77 mg (0.785 mmol) of maleic anhydride in 1 ml of dichloromethane. The mixture took on an orange color which faded away within 15 min. During this period the product precipitated from the solution in nearly quantitative yield. – M.p. 250°C. – $[\alpha]_D$ = –198 (*c* = 0.42, $CHCl_3$). – UV ($CH_3OH$, qualitative): $\lambda_{max}$ = 225 nm. – IR (KBr): $\tilde{\nu}$ = 3057 $cm^{-1}$, 2936, 1859, 1780, 1600, 1090, 921. – $^1$H NMR ($CDCl_3$, 200 MHz): δ = 7.83–7.97 (m, 4H), 7.40–7.57 (m, 3H), 6.40 (d, *J* = 6 Hz, 1H), 6.31 (d, *J* = 6 Hz, 1H), 4.49 (d, *J* = 8 Hz, 1H), 3.50 (d, *J* = 8 Hz, 1H), 2.30 (d, *J* = 13 Hz, 1H), 1.96–2.16 (m, 1H), 1.67–1.83 (m, 1H), 1.12–1.67 (m, 5H), 0.83 (s, 3H), 0.75 (d, *J* = 13 Hz, 1H). – MS (160°C); *m/z* (%) = 358 (19) [$M^+$], 330 (14), 286 (22), 271 (18), 260 (100), 245 (12), 231 (12), 218 (11), 217 (23), 215 (19), 202 (11). – $C_{24}H_{22}O_3$ (358.44): calcd. C 80.42, H 6.19; found C 78.30, H 6.18.

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