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Synthesis of enantiopure angularly condensed [2.2]paracyclophanes containing five-membered rings

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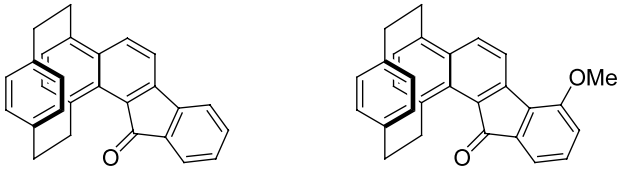
Abstract—Optically active angularly condensed [2.2]paracyclophanes containing five-membered rings have been synthesized by a two-step approach based on the Diels–Alder cycloaddition of (*S*)-(+)-4-vinyl[2.2]paracyclophane. Structural analysis by NMR spectroscopy is presented. These helicenophanes containing a cyclopentane ring show extraordinarily high specific rotations. This phenomenon has been discussed in terms of structural modifications caused by the replacement of the benzene unit with a cyclopentane ring. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

In previous papers we have described the synthesis and structural properties of a variety of optically active angularly condensed [2.2]paracyclophanes.[1,2] Encouraged by these results we sought to develop the synthesis of [2.2]paracyclophane derivatives containing cyclopentane rings. The replacement of a benzene unit with a five-membered carbocyclic ring modifies both the geometry and the electronic properties of the molecules and so may affect the optical properties markedly.

Unpublished preliminary results from our laboratory[3] indicated that optically active helicenophanes **1** and **2**, previously synthesized in racemic form,[4] show very high specific rotation values (Scheme 1). These values are much higher than those shown by other helicenophanes containing six-membered rings only,[1,2] thus emphasizing that the cyclopentane ring gives rise to this phenomenon.



$[\alpha]_D$= +1273 **1**

$[\alpha]_D$= +1314 **2**

Scheme 1.

Furthermore, the replacement of a benzene unit with a cyclopentadiene ring opens the route to the synthesis of optically active metallocenophanes due to the acidity of the methylene hydrogens. These compounds are of special interest since they are optically active, their conductive, magnetic and optical properties may be unusual and additionally they can be polymerised.[5]

Herein, we report the synthesis of some optically active methoxy- and dimethoxy-substituted angularly condensed [2.2]paracyclophanes.

2. Results and discussion

The synthetic approach is based on a previously described[1,2] two-step method in which the Diels–Alder cycloaddition reaction of the (*S*)-(+)-4-vinyl[2.2]-paracyclophane **3**[6] (Scheme 2) with 2-inden-1-ones (e.g. 2-inden-1-one **4a**, 4-methoxy-2-inden-1-one **4b**, 5-methoxy-2-inden-1-one **4c**, 6-methoxy-2-inden-1-one **4d**, 7-methoxy-2-inden-1-one **4e**, 4,5-dimethoxy-2-inden-1-one **4f**, 5,6-dimethoxy-2-inden-1-one **4g**) is the key step. This method based on a Diels–Alder reaction of arylethenes, has also been successfully applied to the synthesis of helicenes.[7]

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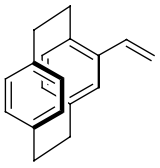
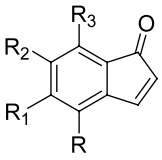


(S)-(+)-**3**



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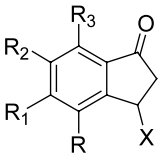


5, X= Br
6, X= H

a, R-R_3=H
b, R= OMe, R_1-R_3= H
c, R_1= OMe, R=R_2=R_3= H
d, R_2= OMe, R=R_1=R_3= H
e, R_3= OMe, R-R_2= H
f, R=R_1= OMe, R_2=R_3= H
g, R_1=R_2= OMe, R=R_3= H

Scheme 2.

In order to shorten the synthesis, the indenones **4** were generated in situ from the corresponding 3-bromoindanones **5** obtained by NBS bromination of the indan-1-ones **6**.[8]

Indanones **6a–d** and **6g** are commercially available; whereas 4,5-dimethoxy-indan-1-one **6f** was prepared according to a known procedure,[9] 7-methoxy-indan-1-one **6e** was prepared by modifying a previous synthesis[10] and improving the total yield from 10 to 27%. Phenol esterification, carried out using commercially available 3-chloropropionyl chloride followed by Fries rearrangement, led to 7-hydroxy-indan-1-one **6e** with a yield (45%) higher than that previously reported in the literature[10] (16.8%).

The cycloaddition reactions were carried out by treating the bromoindanones **5** with $EtAlCl_2$ and then adding diene **3**.[6] The use of $EtAlCl_2$ allowed indenones **4** to be generated in situ from the precursor **5** and also acted as a Lewis acid catalyst in view of the low reactivity of the dienophiles.[11]

The results are summarized in Table 1. The Diels–Alder reactions of indenones **4a**,**b** with *rac*-4-vinyl[2.2]-paracyclophane **3** have been described previously.[4]

Table 1. Experimental conditions of the Diels–Alder reactions of indenones **4**, generated in situ from bromoindanones **5**, with diene **3**[a]

Reactants	Products	Yield (%)
3–5a	**7**	41
3–5b	**8**	44
3–5c	**9**	53
3–5d	**10**	43
3–5e	–	–
3–5f	**11**	64
3–5g	**12**	30

[a] Solvent:toluene; ketone/$EtAlCl_2$ ratio: 0.25; reaction time and temperature: 24 h, reflux.

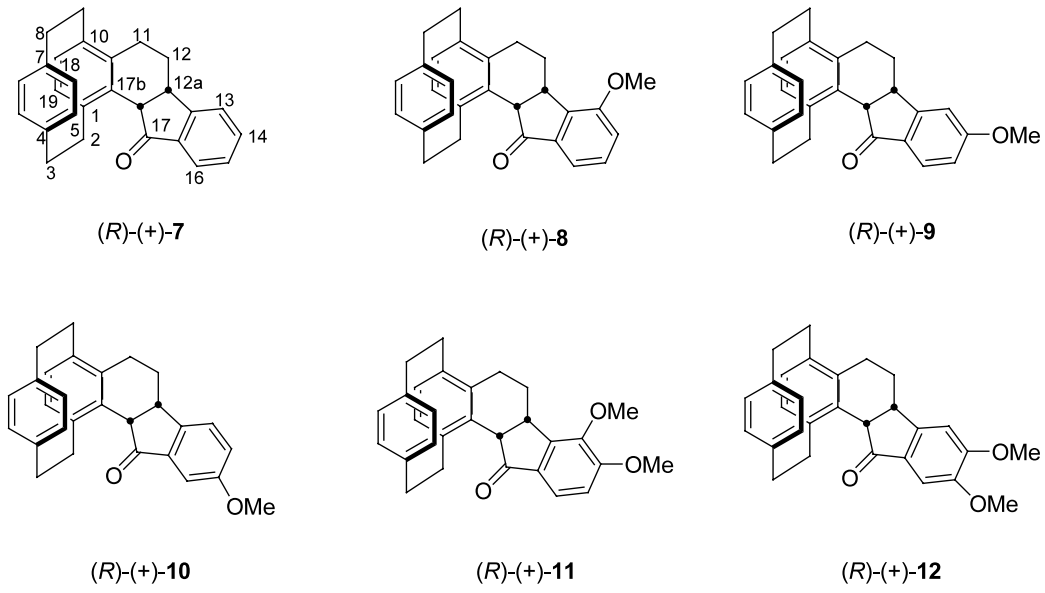
The cycloaddition reactions of indenones **4c–g** with diene (*S*)-(+)-**3** were totally regioselective, *anti*- (with respect to the unsubstituted benzene ring) diastereoselective and occurred in good yields (Scheme 3) except in the case of the cycloaddition reaction with 7-methoxy-2-inden-1-one **4e**. All attempts to carry out the cycloaddition with **4e** failed even though a wide variety of experimental conditions were used. The lack of the reactivity of **4e** probably depends on a combination of two factors: a strong non-bonded repulsive interaction in the transition state between the methoxy group and the ethane bridge methylene hydrogens of the [2.2]paracyclophane unit and a steric interaction between the carbonyl–catalyst complex and the methoxy group in *peri*-like position.

DDQ oxidation of the cycloadducts carried out in toluene at reflux temperature afforded the corresponding optically active helicenophanes **1**, **2**, **13–16** (Table 2, Scheme 4) which were purified and characterized.

Some interesting facts emerge from the data shown in Table 2. Firstly the replacement of a benzene ring with a cyclopentadienone moiety causes an extraordinary increase in the specific rotation values. This indicates that the modification in geometry and, consequently, in the electronic structure of the helical angularly condensed ring portion of the aromatised molecules, plays a fundamental role in determining the observed specific rotation values. Indeed, the specific rotation values are comparable to those observed with helicenes[12] and much higher than those of [2.2]paracyclophane derivatives.[13]

Secondly, the same phenomenon is not observed in the cycloadducts, where the specific rotations are markedly smaller than those of aromatised molecules; this is in agreement with a previous comment.

Thirdly, although all helicenophanes show high specific rotation values, those of compounds **14** and **16** are extraordinarily high. This is the most interesting fact



Scheme 3.

Table 2. Reaction products of DDQ oxidation of cycloadducts **7**–**12**[a] and their specific rotation values

Cycloadduct	Product	Yield (%)	$[\alpha]_D$
7	**1**	85[b]	+1273
8	**2**	73[b]	+1314
9	**13**	75	+1093
10	**14**	80	+1692
11	**15**	78	+1040
12	**16**	70	+1952

[a] Solvent:toluene; reaction time and temperature: 8 h, reflux.
[b] The oxidation of cycloadducts **7** and **8** in racemic form has already been described.[4]

and points out a close relationship between the position of the methoxy group in the benzene ring and the chiroptical properties. The presence of the methoxy group at the 15 position seems to play a crucial role in increasing the specific rotation.

2.1. Structural analysis

The structure of compounds **1**, **2**, **7**, **8** were assigned previously on racemic ketones.[4] The structure of the ketones **9**–**16** was inferred from the analysis of their high-field ^1H and ^{13}C NMR spectra. The pertinent data are collected in Section 4.

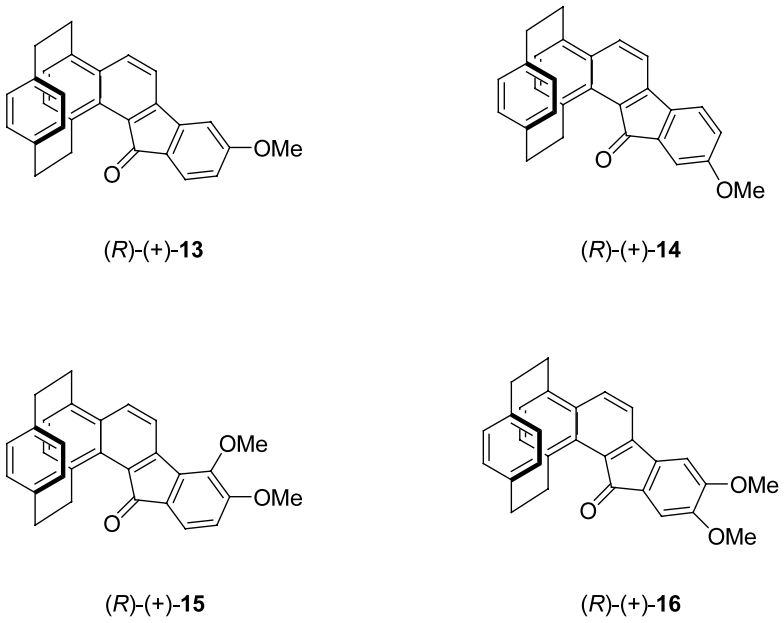
The position of the carbonyl function of cycloadducts **9**–**12** follows from the observation that C(16)H gives long-range heterocorrelation with the C(17) carbonyl carbon, and also from the NOE enhancement on C(12a)H observed for **9**, **10** and **12** upon selective pre-irradiation of the C(13)H resonance. The *cis*-relationship of C(12a)H and C(17a)H for cycloadducts **9**–**12** follows from the NOEs observed between them. Further support for this stereochemical assignment is given by the $^3J_{12a,17a}$ values, i.e. 6.6 Hz for **9**, 6.9 Hz for **10**, 6.8 Hz for **11** and **12**. Furthermore, the NOEs observed between C(5)H and C(17a)H for **9**–**12** show that C(17a)H points toward the unsubstituted benzene ring of the paracyclophane unit, as shown in Fig. 1 for cycloadduct **12**, reported as an example.

This indicates a total *anti*-diastereoselectivity in the cycloaddition reaction between diene **3** and the indenones **4**.

The structure determination of the ketones **13**–**16** is based on the known outcome of the procedure used to dehydrogenate the cycloadducts and is confirmed by the $^1H\{^1H\}$ NOE experiments summarized in Fig. 1 for ketone **16** (reported as an example).

The NOEs observed on the C(12)H resonance of compounds **13**, **14** and **16** upon selective irradiation of the resonances attributed to the C(11)H and C(13)H protons confirm the position of the carbonyl function; in the case of compound **15**, an NOE is observed between C(11)H and C(12)H. This regiochemical assignment is also in agreement with the unusual downfield shift of the C(2) protons ($\delta = 4.44$–4.52 for **13**–**16**), due to the anisotropic effect of the carbonyl group (Fig. 1).

Further support for the structure of **13**–**16** is provided by the NOE effect observed for C(9)H upon irradiation of C(11)H. In the case of compound **14**, an NOE is also observed on C(14)H upon irradiation of C(13)H; finally, for compound **16** NOEs are also observed for the C(14) and C(15) methoxy group protons upon selective irradiation of C(13)H and C(16)H, respectively.



Scheme 4.

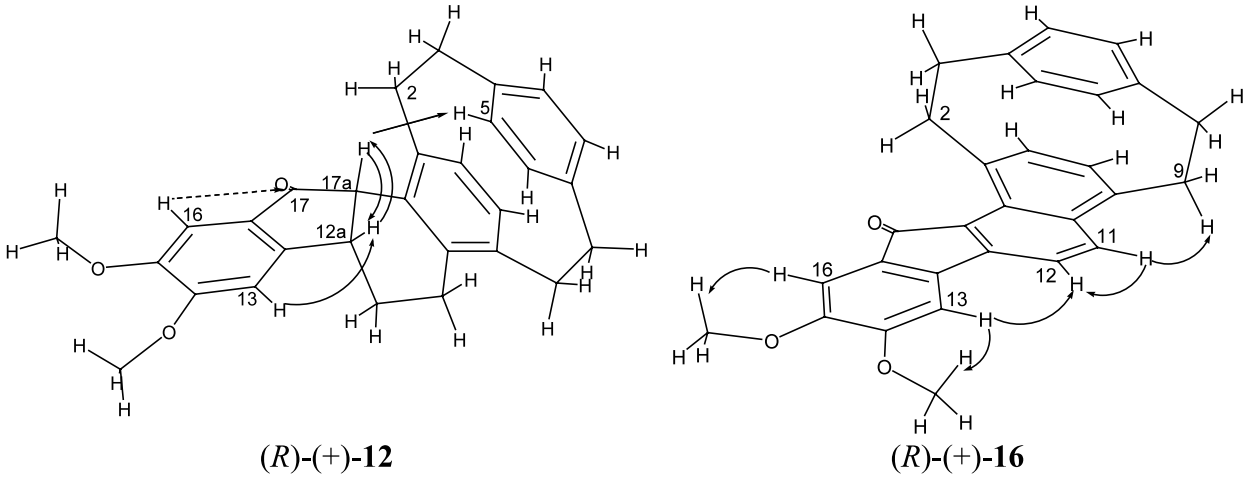


Figure 1. Minimized energy conformations of compounds **12** and **16**; the arrows indicate observed NOEs; dotted arrows indicate long-range hetero-correlations.

3. Conclusions

Several optically active angularly condensed [2.2]paracyclophanes containing five-membered rings have been synthesized by a two-step approach based on the Diels–Alder reaction of (*S*)-(+)-4-vinyl[2.2]-paracyclophane **3**. The Diels–Alder reactions have been shown to occur regioselectively and *anti*-diastereoselectively. The most important result which emerges from this study is that this type of helicenophanes shows extraordinarily high specific rotation values and this fact depends on both the distortion and the modified electronic structure of the helical condensed portion of the molecule due to the replacement of the benzene unit with a cyclopentadienone moiety. The position of the methoxy substituents on the benzene ring also seems to have an important influence on the specific rotation values.

Further studies on the synthesis of helicenophanes containing two carbocyclic five-membered rings are currently in progress.

4. Experimental

4.1. General

Melting points (uncorrected) were determined on a Büchi melting point apparatus. Optical rotations were measured on a Jasco DIP-360 polarimeter in a quartz-cell at 25°C in $CHCl_3$ solution.

Gas chromatographic analyses were performed on Hewlett–Packard 6890 chromatograph. IR spectra were recorded in $CHCl_3$ solution at room temperature on a

Perkin Elmer Paragon 500 FT-IR. Absorption chromatography was carried out on Merck silica gel (0.040–0.063 mm, 230–400 mesh). Mass spectra were observed on a Hewlett-Packard 5970 GC–MS instrument at 70 eV. The NMR spectra were recorded on a Bruker AC 200 and on a Varian Associates VXR-400 multinuclear instrument in $CDCl_3$ solution (TMS as internal reference); ^1H and ^{13}C shift assignments were based on COSY, $^1H\{^1H\}$NOE, and HETCOR experiments. The signals with the same superscripts 'a' or 'b' in the ^1H and ^{13}C spectra may be interchanged.

A commercially available 1 M hexane solution of ethyl aluminum dichloride was used; toluene was distilled from Na and $LiAlH_4$. Commercial *N*-bromosuccinimide was freshly crystallized from water before use. Commercial indanones **6c** and **6g** were purified by column chromatography (eluting with 4:1 hexane/ethyl acetate) before use.

4.2. 7-Hydroxy-indan-1-one

A mixture of phenol (6.8 g, 72 mmol) and 3-chloropropionyl chloride (6.9 ml, 72 mmol) was stirred at 90°C for 2.5 h. The mixture was then cooled to room temperature, then $AlCl_3$ (44 g) was added and the mixture stirred at 100°C for 1 h and at 160°C for 2 h. The reaction mixture was then cooled to 0°C and conc. hydrochloric acid was added and the resulting slurry was extracted with CH_2Cl_2. After evaporation of the solvent, the residue was chromatographed on silica gel (elution with 6:4 CH_2Cl_2/hexane) to afford pure 7-hydroxy-indan-1-one as a white solid (4.8 g, 45%, lit.[10a] 17% yield); mp 110–111°C (methanol); IR 1678 (s, C=O) cm^{-1}; ^1H NMR (200 MHz) δ 2.63 (m, 2H, H_s-3), 3.09 (m, 2H, H_s-2), 6.82 (m, 2H, H-4, H-5), 7.44 (t, 1H, $J=7.8$ Hz, H-6), 9.04 (s, 1H, OH).

4.3. 7-Methoxy-indan-1-one, 6e

A mixture of DMSO (10 ml) and powdered KOH (0.6 g, 10.5 mmol) was stirred for 5 min at room temperature. Then 7-hydroxy-indan-1-one (0.73 g, 5.34 mmol) and CH_3I (0.66 ml, 10.7 mmol) were added[10b] to the mixture at 5°C. The resulting solution was stirred for 20 min at room temperature and then poured in water and extracted with CH_2Cl_2. The organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography of the residue on silica gel eluting with 9:1 CH_2Cl_2/ethyl acetate afforded 0.48 g (60%) of pure **6e** as a white solid; mp 102–103°C (pentane/ethyl acetate); ^1H NMR (200 MHz) δ 2.64 (m, 2H, H_s-3), 3.05 (m, 2H, H_s-2), 3.92 (s, 3H, OMe), 6.87 (m, 2H, H-4, H-5), 7.49 (t, 1H, $J=8.1$ Hz, H-6).

4.4. General procedure for the bromination reaction of indan-1-ones 6

NBS (1 mmol) and AIBN (0.01 mmol) were added to a CCl_4 solution (1.7 ml) of the indan-1-ones **6** (1 mmol). The resulting mixture was stirred at reflux temperature for 2.5 h, then cooled and filtered through Celite, which was then washed with CCl_4. The filtrate was washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo to afford the 3-bromo-indan-1-ones **5**.

4.4.1. Compound 5c. (87%); ^1H NMR δ 3.02 (dd, 1H, $J=19.6$, 2.8 Hz, H-2), 3.34 (dd, 1H, $J=19.6$, 7.1 Hz, H-2), 3.91 (s, 3H, OMe), 5.52 (dd, 1H, $J=7.1$, 2.8 Hz, H-3), 7.03 (m, 2H, Ar-H), 7.66 (d, 1H, $J=8.5$ Hz, Ar-H).

4.4.2. Compound 5d. (91%); ^1H NMR δ 3.06 (dd, 1H, $J=19.8$, 2.2 Hz, H-2), 3.37 (dd, 2H, $J=19.8$, 6.9 Hz, H-2), 3.84 (s, 3H, OMe), 5.57 (dd, 1H, $J=6.9$, 2.2 Hz, H-3), 7.20 (m, 2H, Ar-H), 7.57 (m, 1H, Ar-H).

4.4.3. Compound 5e. (84%); ^1H NMR (200 MHz) δ 2.94 (m, 2H, Hs-2), 3.93 (s, 3H, OMe), 7.23 (m, 3H, Ar-H).

4.4.4. Compound 5f. (98%); ^1H NMR δ 3.22 (m, 2H, Hs-2), 3.97 (s, 3H, OMe), 4.06 (s, 3H, OMe), 5.63 (m, 1H, H-3), 6.95 (d, 1H, $J=8.4$ Hz, Ar-H), 7.53 (d, 1H, $J=8.4$ Hz, Ar-H).

4.4.5. Compound 5g. (97%); ^1H NMR δ 3.04 (dd, 1H, $J=19.6$, 2.4 Hz, H-2), 3.36 (dd, 1H, $J=19.6$, 6.8 Hz, H-2), 3.93 (s, 3H, OMe), 4.00 (s, 3H, OMe), 5.56 (dd, 1H, $J=6.8$, 2.5 Hz, H-3), 7.07 (s, 1H, Ar-H), 7.15 (s, 1H, Ar-H).

4.5. General procedure for the Diels–Alder reaction between the 3-bromoindanones 5 and (*S*)-(+)-4-vinyl[2.2]paracyclophane 3

A solution of $EtAlCl_2$ (1 M, 0.25 ml, 0.25 mmol) was added to a toluene (5 ml) solution of 3-bromoindanones **5** (1.1 mmol) and the resulting mixture was stirred at room temperature for 30 min under nitrogen. Then a toluene (2 ml) solution of diene **3** (0.23 g, 1 mmol) was added and the mixture was heated at reflux temperature for 24 h under nitrogen. After usual workup the residue was chromatographed on silica gel with 9:1 hexane/ethyl acetate to afford pure cycloadducts **7**–**12** (Table 1).

4.5.1. Compound (*R*)-(+)-7. White plates; mp 151–152°C (hexane/ethyl acetate, 3:1); $[\alpha]_D=+346$ (*c* 1.73).

4.5.2. Compound (*R*)-(+)-8. White plates; mp 214–215°C (hexane/ethyl acetate, 3:1); $[\alpha]_D=+315$ (*c* 0.26).

4.5.3. Compound (*R*)-(+)-9. White plates; mp 144–145°C (hexane/ethyl acetate, 3:1); $[\alpha]_D=+230$ (*c* 0.55); IR 1709 (s, C=O) cm^{-1}; ^1H NMR δ 1.11 (ddd, 1H, $J=12.7$, 12.1, 4.1 Hz, H-12), 2.30 (m, 1H, H-12), 2.41 (m, 1H, H-11), 2.73 (m, 1H, H-11), 2.77–3.50 (m, 8H, H_s-2, H_s-3, H_s-8, H_s-9), 3.52 (ddd, 1H, $J=12.1$, 6.6, 4.4 Hz, H-12a), 3.63 (br. d, 1H, $J=6.6$ Hz, H-17a), 3.92 (s, 3H, OMe), 6.42 (d, 1H, $J=7.8$ Hz, H-19), 6.48 (dd, 1H, $J=7.8$, 1.8 Hz, H-5), 6.56 (dd, 1H, $J=7.8$, 1.8 Hz, H-21), 6.58 (d, 1H, $J=7.8$ Hz, H-18), 6.60 (dd, 1H, $J=7.8$, 1.9 Hz, H-20), 6.79 (dd, 1H, $J=7.8$, 1.9 Hz, H-6), 6.92 (dd, 1H $J=8.5$, 2.30 Hz, H-15), 7.00 (d, 1H, $J=2.3$ Hz, H-13), 7.70 (d, 1H, $J=8.5$ Hz, H-16); ^{13}C NMR δ 27.8 (C-11), 31.4 (C-12), 32.8, 33.7, 33.73, 33.8 (C-2, C-3, C-8, C-9), 39.2

(C-12a), 52.0 (C-17a), 55.9 (OMe), 109.2 (C-13), 115.3 (C-15), 126.5 (C-16), 127.0 (C-6), 128.0 (C-16a), 128.1 (C-5), 131.0 (C-1), 132.1 (C-19), 132.3 (C-18), 133.4, 133.8 (C-20, C-21), 136.0 (C-17b), 138.2 (C-4), 139.3 (C-10), 139.7 (C-7), 140.1 (C-10a), 160.3 (C-12b), 165.3 (C-14), 200.5 (C-17); MS, *m*/*e* (rel. intensity) 394 (M+, 100), 291 (9), 290 (39), 289 (15), 275 (19), 247 (6), 207 (14), 202 (6), 104 (7). Anal. calcd for $C_{28}H_{26}O_2$: C, 85.25; H, 6.64. Found: C, 85.2; H, 6.5%.

4.5.4. Compound (*R*)-(+)-10. White plates; mp 223–224°C (CH_2Cl_2/hexane, 1:3); $[\alpha]_D = +318$ (*c* 1.21); IR 1712 (s, C=O) cm^{-1}; ^1H NMR δ 1.04 (ddd, 1H, $J = 12.6$, 12.3, 4.3 Hz, H-12), 2.29 (m, 1H, H-12), 2.42 (m, 1H, H-11), 2.74 (m, 1H, H-11), 2.75–3.50 (m, 8H, H_s-2, H_s-3, H_s-8, H_s-9), 3.51 (ddd, 1H, $J = 12.3$, 6.9, 4.5 Hz, H-12a), 3.65 (br. d, 1H, $J = 6.9$ Hz, H-17a), 3.84 (s, 3H, OMe), 6.44 (d, 1H, $J = 7.8$ Hz, H-19), 6.49 (dd, 1H, $J = 7.9$, 1.8 Hz, H-5), 6.57 (dd, 1H, $J = 7.9$, 1.8 Hz, H-21), 6.60 (d, 1H, $J = 7.8$ Hz, H-18), 6.61 (dd, 1H $J = 7.9$, 1.8 Hz, H-20), 6.80 (dd, 1H, $J = 7.9$, 1.8 Hz, H-6), 7.21–7.22 (m, 2H, H-14, H-16), 7.48 (d, 1H, $J = 8.8$ Hz, H-13); ^{13}C NMR δ 27.9 (C-11), 31.8 (C-12), 32.8, 33.6_9, 33.7 (C-2, C-3, C-8, C-9), 38.6 (C-12a), 52.7 (C-17a), 55.8 (OMe), 106.4 (C-16), 123.6 (C-14), 126.1 (C-13), 127.1 (C-6), 128.1 (C-5), 130.9 (C-1), 132.2 (C-19), 132.2_4 (C-18), 133.4, 133.8 (C-20, C-21), 136.0 (C-17b), 136.2 (C-16a), 138.3 (C-4), 139.3 (C-10), 139.6 (C-7), 140.4 (C-10a), 150.4 (C-15), 160.0 (C-12b), 202.3 (C-17); MS, *m*/*e* (rel. intensity) 394 (M+, 100), 291 (8), 290 (36), 289 (12), 275 (18), 262 (6), 247 (8), 202 (6). Anal. calcd for $C_{28}H_{26}O_2$: C, 85.25; H, 6.64. Found: C, 85.3; H, 6.6%.

4.5.5. Compound (*R*)-(+)-11. White plates; mp 204–205°C (hexane/ethyl acetate, 3:1); $[\alpha]_D = +323$ (*c* 0.50); IR 1716 (s, C=O) cm^{-1}; ^1H NMR δ 0.97 (dddd, 1H, $J = 13.0$, 12.1, 11.0, 4.1 Hz, H-12), 2.39 (m, 1H, H-12), 2.43 (m, 1H, H-11), 2.80–3.46 (m, 9H, H_s-2, H_s-3, H_s-8, H_s-9, H-11), 3.55 (brd, 1H, $J = 6.8$ Hz, H-17a), 3.69 (ddd, 1H, $J = 11.0$, 6.8, 4.0 Hz, H-12a), 3.97 (s, 3H, 13-OMe), 4.05 (s, 3H, 14-OMe), 6.43 (d, 1H, $J = 7.6$ Hz, H-19), 6.49 (dd, 1H, $J = 7.8$, 1.8 Hz, H-5), 6.56 (dd, 1H, $J = 7.8$, 1.8 Hz, H-21), 6.60 (d, 1H, $J = 7.6$ Hz, H-18), 6.61 (dd, 1H, $J = 7.8$, 1.8 Hz, H-20), 6.85 (dd, 1H, $J = 7.8$, 1.8 Hz, H-6), 6.98 (d, 1H, $J = 8.2$ Hz, H-15), 7.54 (d, 1H, $J = 8.2$ Hz, H-16); ^{13}C NMR δ 28.1 (C-11), 30.1 (C-12), 32.8, 33.7 (C-2, C-3, C-8, C-9), 36.4 (C-12a), 52.2 (C-17a), 56.4 (13-OMe). 61.3 (14-OMe), 112.7 (C-15), 121.2 (C-16), 127.0 (C-6), 128.0 (C-5), 128.8 (C-16a), 130.9 (C-1), 132.0 (C-19), 133.4, 133.8 (C-18, C-20, C-21), 136.1 (C-17b), 138.3 (C-4), 139.3 (C-10), 139.6 (C-7), 140.4 (C-10a), 145.6 (C-13), 150.0 (C-12b), 157.7 (C-14), 200.6 (C-17); MS, *m*/*e* (rel. intensity) 424 (M+, 100), 321 (11), 320 (36), 319 (12), 305 (11), 281 (24) 208 (19), 207 (89), 191 (13), 73 (15). Anal. calcd for $C_{29}H_{28}O_3$: C, 85.05; H, 6.65. Found: C, 85.0; H, 6.5%.

4.5.6. Compound (*R*)-(+)-12. White plates; mp 245–246°C (CH_2Cl_2/hexane, 1:3); $[\alpha]_D = +302$ (*c* 0.20); IR 1700 (s, C=O) cm^{-1}; ^1H NMR: δ 1.10 (dddd, 1H, $J = 12.9$, 12.4, 12.0, 4.0 Hz, H-12), 2.31 (m, 1H, H-12), 2.42 (ddd, 1H, $J = 16.4$, 12.4, 4.0 Hz, H-11), 2.73 (m, 1H, H-11), 2.81–3.50 (m, 8H, Hs-2, Hs-3, Hs-8, Hs-9), 3.50 (ddd, 1H, $J = 12.0$, 6.8, 4.4 Hz, H-12a), 3.90 (s, 3H, 15-OMe), 4.03 (s, 3H, 14-OMe), 6.42 (d, 1H, $J = 7.8$ Hz, H-19), 6.50 (dd, 1H, $J = 7.9$, 1.6 Hz, H-5), 6.57[a] (dd, 1H, $J = 7.8$, 1.6 Hz, H-21), 6.59 (d, 1H, $J = 7.8$ Hz, H-18), 6.62[a] (dd, 1H, $J = 7.8$, 1.6 Hz, H-20), 6.78 (dd, 1H, $J = 7.9$, 1.6 Hz, H-6), 7.00 (s, 1H, H-13), 7.21 (s, 1H, H-16); ^{13}C NMR: δ 27.6 (C-11), 31.4 (C-12), 32.6, 33.4_9, 33.5_4, 33.6 (C-2, C-3, C-8, C-9), 38.7 (C-12a), 51.8 (C-17a), 56.2 (14-OMe), 56.3 (15-OMe), 105.3 (C-16), 106.4 (C-13), 126.9 (C-6), 127.3 (C-16a), 127.9 (C-5), 130.9 (C-1), 131.9 (C-19), 132.1 (C-18), 133.2, 133.6 (C-20, C-21), 135.8 (C-17b), 138.0 (C-10), 139.1, 139.5 (C-4, C-7), 140.3 (C-10a), 149.7 (C-15), 152.4 (C-14), 155.2 (C-12b), 200.9 (C-17); MS, *m*/*e* (rel. intensity) 424 (M+, 100), 321 (7), 320 (31), 305 (10), 289 (8), 104 (6). Anal. calcd for $C_{29}H_{28}O_3$: C, 85.05; H, 6.65. Found: C, 84.9; H, 6.7%.

4.6. General procedure for the DDQ oxidation of cycloadducts 9–12

A toluene (7 ml) solution of cycloadducts **9**–**12** (1 mmol) and DDQ (4 mmol) was heated at reflux temperature for 8 h. After cooling, the solvent was removed in vacuo and the residue was chromatographed on silica gel (elution with 95:5 hexane/ethyl acetate) to afford pure compounds **13**–**16**.

4.6.1. Compound (*R*)-(+)-1. Red–orange crystals; mp 224–225°C (hexane/ethyl acetate, 3:1); $[\alpha]_D = +1273$ (*c* 0.35).

4.6.2. Compound (*R*)-(+)-2. Red–orange crystals; mp 278–279°C (hexane/ethyl acetate, 3:1); $[\alpha]_D = +1314$ (*c* 0.16).

4.6.3. Compound (*R*)-(+)-13. Pale orange crystals; mp 160–161°C (CH_2Cl_2/hexane, 1:3); $[\alpha]_D = +1093$ (*c* 0.59); IR 1725 (s, C=O) cm^{-1}; ^1H NMR δ 2.72 (m, 1H, H-3), 2.94 (m, 1H, H-8), 2.95 (m, 1H, H-3), 3.03 (m, 1H, H-9), 3.10 (m, 1H, H-2), 3.19 (m, 1H, H-8), 3.73 (m, 1H, H-9), 3.84 (s, 3H, OMe), 4.52 (m, 1H, H-2), 5.74 (dd, 1H, $J = 7.8$, 1.6 Hz, H-6), 5.78 (dd, 1H, $J = 7.8$, 1.6 Hz, H-5), 6.54[b] (dd, 1H, $J = 8.0$, 1.6 Hz, H-21), 6.57[b] (dd, 1H, $J = 8.0$, 1.6 Hz, H-20), 6.65 (d, 1H, $J = 7.3$ Hz, H-18), 6.72 (dd, 1H, $J = 8.2$, 2.3 Hz, H-15), 6.84 (d, 1H, $J = 7.3$ Hz, H-19), 7.06 (d, 1H, $J = 2.3$ Hz, H-13), 7.57 (d, 1H, $J = 8.3$ Hz, H-12), 7.58 (d, 1H, $J = 8.2$ Hz, H-16), 7.87 (d, 1H, $J = 8.3$ Hz, H-11); ^{13}C NMR δ 33.6 (C-9), 34.6 (C-8), 35.0 (C-3), 37.4 (C-2), 56.0 (OMe), 107.2 (C-13), 112.6 (C-15), 117.0 (C-12), 125.9 (C-16), 127.6 (C-16a), 128.4, 130.0 (C-5, C-6), 130.8 (C-17a), 131.4 (C-17b), 131.9[a] (C-20), 132.1 (C-18), 132.6 (C-11), 132.7[a] (C-21), 136.3 (C-19), 137.1[b] (C-1), 137.4 (C-10), 137.8 (C-7), 138.2 (C-10a), 139.8 (C-4), 144.5[b] (C-12a), 146.3[b] (C-12b), 165.3 (C-14), 192.6 (C-17); MS, *m*/*e* (rel. intensity) 390 (M+, 31), 287 (24), 286 (10), 285 (42), 243 (8), 242 (11), 213 (7). Anal. calcd for $C_{28}H_{22}O_2$: C, 86.13; H, 5.68. Found: C, 86.1; H, 5.7%.

4.6.4. Compound (*R*)-(+)-14. Red–orange crystals; mp 278–279°C (CH_2Cl_2/hexane, 1:3); $[\alpha]_D = +1692$ (*c* 0.15); IR 1701 (s, C=O) cm^{-1}; ^1H NMR δ 2.71 (m, 1H, H-3), 2.94 (m, 1H, H-8), 2.96 (m, 1H, H-3), 3.03 (m, 1H, H-9), 3.12 (m, 1H, H-2), 3.18 (m, 1H, H-8), 3.72 (m, 1H, H-9), 3.88 (s, 3H, OMe), 4.45 (m, 1H, H-2), 5.80 (m, 2H, H-5, H-6), 6.54[a] (dd, 1H, *J* = 7.9, 1.6 Hz, H-21), 6.57[a] (dd, 1H, *J* = 7.9, 1.6 Hz, H-20), 6.65 (d, 1H, *J* = 7.3 Hz, H-18), 6.82 (d, 1H, *J* = 7.3 Hz, H-19), 6.93 (dd, 1H, *J* = 8.1, 2.4 Hz, H-14), 7.18 (d, 1H, *J* = 2.4 Hz, H-16), 7.39 (d, 1H, *J* = 8.1 Hz, H-13), 7.50 (d, 1H, *J* = 8.4 Hz, H-12), 7.85 (d, 1H, *J* = 8.4 Hz, H-11), ^{13}C NMR δ 33.6 (C-9), 34.0 (C-8), 35.0 (C-3), 37.2 (C-2), 56.0 (OMe), 110.0 (C-16), 116.9 (C-12), 119.1 (C-14), 120.8 (C-13), 128.3[a] (C-6), 129.4 (C-17a), 130.0[a] (C-5), 131.6 (C-17b), 131.8 (C-18), 132.0[b] (C-20), 132.2[b] (C-21), 133.5 (C-11), 136.2 (C-12b), 136.5 (C-19), 136.6 (C-16a), 137.0 (C-10a), 137.2, 137.3 (C-1, C-10), 137.8 (C-7), 139.7 (C-4), 146.7 (C-12a), 161.4 (C-15), 193.4 (C-17); MS, *m*/*e* (rel. intensity) 390 (M+, 28), 287 (22), 286 (100), 285 (40), 243 (8), 242 (8), 213 (7). Anal. calcd for $C_{28}H_{22}O_2$: C, 86.13; H, 5.68. Found: C, 86.0; H, 5.7%.

4.6.5. Compound (*R*)-(+)-15. Pale orange crystals; mp 211–212°C (CH_2Cl_2/hexane, 1:3); $[\alpha]_D = +1040$ (*c* 0.45); IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 2.74 (m, 1H, H-3), 2.92 (m, 2H, H-3, H-8), 3.04 (m, 1H, H-9), 3.10 (m, 1H, H-2), 3.20 (m, 1H, H-8), 3.75 (m, 1H, H-9), 3.96 (s, 3H, 13-OMe), 4.05 (s, 3H, 14-OMe), 4.44 (m, 1H, H-2), 5.75 (dd, 1H, *J* = 7.8, 1.7 Hz, H-5), 5.81 (dd, 1H, *J* = 7.8, 1.7 Hz, H-6), 6.56[a] (dd, 1H, *J* = 7.9, 1.7 Hz, H-21), 6.58[a] (dd, 1H, *J* = 7.9, 1.7 Hz, H-20), 6.67 (d, 1H, *J* = 7.2 Hz, H-18), 6.72 (d, 1H, *J* = 8.0 Hz, H-15), 6.84 (d, 1H, *J* = 7.2 Hz, H-19), 7.38 (d, 1H, *J* = 8.0 Hz, H-16), 7.89 (d, 1H, *J* = 8.3 Hz, H-11), 8.02 (d, 1H, *J* = 8.3 Hz, H-12); ^{13}C NMR δ 33.6 (C-9), 34.6 (C-8), 35.1 (C-3), 37.4 (C-2), 56.4 (13-OMe), 60.8 (14-OMe), 111.3 (C-15), 120.7 (C-12), 121.0 (C-16), 128.3 (C-5), 128.7 (C-16a), 130.1 (C-6), 130.5 (C-17a), 131.3 (C-17b), 131.9[a] (C-20), 132.1[a] (C-21), 132.1_4 (C-18), 132.8 (C-11), 135.3 (C-12b), 136.2 (C-19), 136.9, 137.3, 137.7, 137.8 (C-1, C-7, C-10, C-10a), 139.7 (C-4), 144.1 (C-13), 144.9 (C-12a), 159.0 (C-14), 192.3 (C-17); MS *m*/*e* (rel. intensity) 420 (M+, 32), 317 (25), 316 (100), 315 (10), 272 (6), 271 (7). Anal. calcd for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75. Found: C, 82.8; H, 5.7%.

4.6.6. Compound (*R*)-(+)-16. Red–orange crystals; mp 254–255°C (CH_2Cl_2/hexane, 1:3); $[\alpha]_D = +1952$ (*c* 0.14); IR 1714 (s, C=O) cm^{-1}; ^1H NMR: δ 2.73 (m, 1H, H-3), 2.91 (m, 1H, H-8), 2.96 (m, 1H, H-9), 3.0 (m, 1H, H-3), 3.13 (m, 1H, H-2), 3.18 (m, 1H, H-8), 3.71 (m, 1H, H-9), 3.94 (s, 3H, 15-OMe), 4.03 (s, 3H, 14-OMe), 4.50 (m, 1H, H-2), 5.79 (dd, 1H, *J* = 7.8, 1.7 Hz, H-6), 5.81 (dd, 1H, *J* = 7.8, 1.7 Hz, H-5), 6.55[a] (dd, 1H, *J* = 7.8, 1.7 Hz, H-21), 6.57[a] (dd, 1H, *J* = 7.8, 1.7 Hz, H-20), 6.63 (d, 1H, *J* = 7.2 Hz, H-18), 6.81 (d, 1H, *J* = 7.2 Hz, H-19), 7.02 (s, 1H, H-13), 7.16 (s, 1H, H-16), 7.46 (d, 1H, *J* = 8.2 Hz, H-12), 7.81 (d, 1H, *J* = 8.2 Hz, H-11); ^{13}C NMR: δ 33.4 (C-9), 34.4 (C-8), 34.8 (C-3), 37.1 (C-2), 56.3 (14-OMe), 56.4 (15-OMe), 103.4 (C-13), 107.6 (C-16), 116.3 (C-12), 127.2 (C-16a), 128.1 (C-6), 129.6[a] (C-10a), 129.8 (C-5), 131.3 (C-17b), 131.5, 131.8 (C-20, C-21), 131.9 (C-18), 132.6 (C-11), 136.2 (C-19), 136.8[a] (C-1), 136.9[a] (C-10), 137.5 (C-12b), 137.6[a] (C-7), 138.2 (C-17a), 139.5[a] (C-4), 145.2 (C-14), 149.9 (C-15), 154.0 (C-12a), 193.0 (C-17); MS, *m*/*e* (rel. intensity) 420 (M+, 31), 317 (24), 316 (100), 315 (21), 301 (6), 273 (6), 229 (6). Anal. calcd for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75. Found: C, 82.8; H, 5.8%.

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