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(*R*)- and (*S*)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone as chiral auxiliaries in Diels–Alder reactions

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Abstract

A study of the Diels–Alder reactions of the esters derived from acrylic, methacrylic, *trans*-crotonic and *trans*-cinnamic acid and the chiral auxiliaries (*R*)- and/or (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone (**4**, **17**, **25** and **26**, respectively) with different dienes [cyclopentadiene **5**, isoprene **8**, 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene **9** and anthracene **10**], catalyzed by titanium tetrachloride, is described. Cyclopentadiene gave adducts with esters (*R*)- or (*S*)-**4** and (*R*)-**25** with high *endo*- and *facial*-diastereoselectivities. Diene **5** reacted with (±)-**17** without *endo*-diastereoselectivity and failed to give a cycloadduct with (±)-**26**. Isoprene reacted only with ester (*S*)-**4** with high *facial*-diastereoselectivity. The reaction of **9** with (*R*)-**4** failed, because the diene was not stable under the acid reaction conditions. Adducts derived from **10** and esters (*S*)-**4** and (*R*)-**17** could be obtained with high *facial*-diastereoselectivity. LiOH-hydrolysis of the adducts derived from esters (*R*)- or (*S*)-**4** and (*R*)-**25** gave the corresponding enantiopure acids, the chiral auxiliaries being completely recovered unchanged. However, hydrolysis of the adduct derived from **10** and (*R*)-**17**, required more drastic basic conditions which partially epimerized the chiral auxiliary. X-Ray diffraction analysis of the adducts derived from **10** and esters (*S*)-**4** and (*R*)-**17**, let us establish their relative configurations and, taking into account the absolute configuration of the starting chiral auxiliary, their absolute configurations.

1. Introduction

Some time ago, we described[1] a multigram scale synthesis of both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- and (*S*)-**1**, and their use for the formal deracemization of α-arylpropanoic acids,[2] α-substituted α-arylacetic acids,[3] α-chloro acids,[4] and α-amino acids.[5] Also,

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we described their use in an enantioselective synthesis of α-hydroxy acids,[6] α-aryloxypropanoic acid herbicides,[4] such as dichlorprop-P and mecoprop-P, and α-amino acids,[5] based on the dynamic kinetic resolution of α-bromo esters derived from these chiral auxiliaries on reaction with different nucleophiles. A key-point of these transformations is the efficient recovery of the chiral auxiliaries, which are easily crystallizable non-hygroscopic solids.

Much work has been done in the last two decades to develop asymmetric Diels–Alder reactions, based on both enantiopure dienes[7–9] and enantiopure dienophiles.[10–23] In the present decade, interest had progressively shifted towards catalyzed enantioselective Diels–Alder reactions.[24–35]

The acrylate of D-pantolactone has been reacted with high *facial*-diastereoselectivity with dienes **5**,[11] **8**,[11] **10**,[13] and a 5-substituted cyclopentadiene,[19] under $TiCl_4$ catalysis. Also, an (*E*)-2-cyanocinnamate derived from D-pantolactone has been reacted with high *endo*- and *facial*-diastereoselectivities with cyclopentadiene[20] and butadiene.[23]

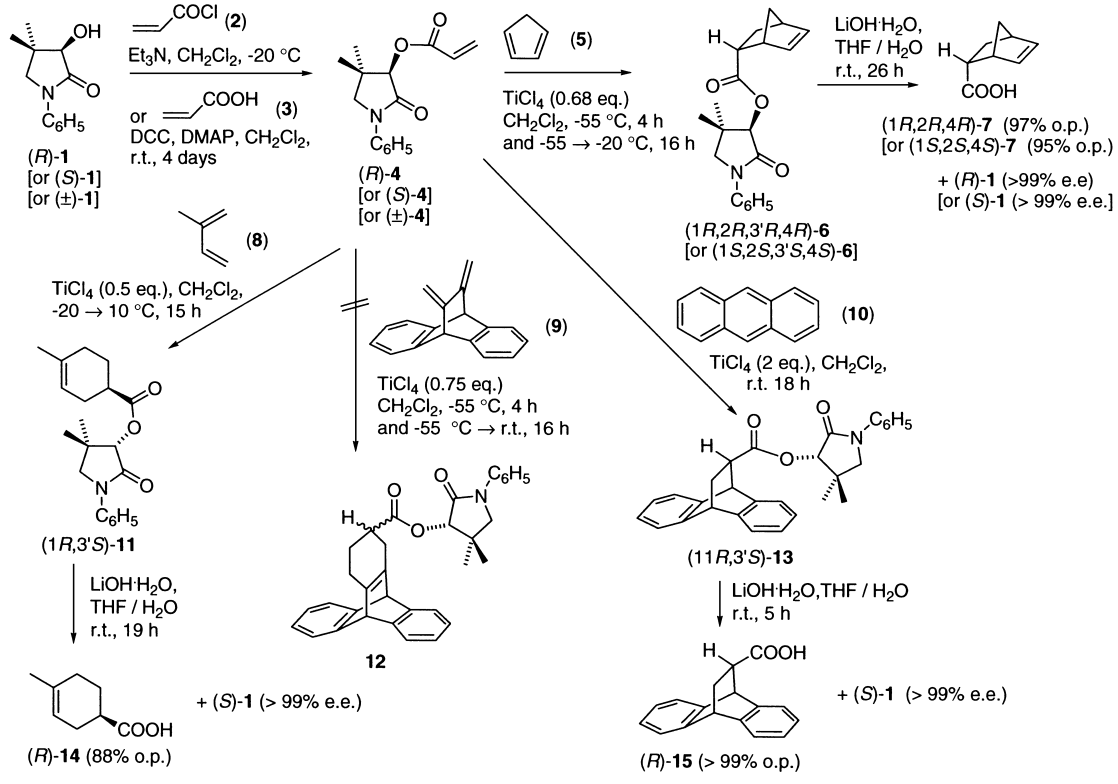
Since (*R*)-pantolactone is a hygroscopic compound and its (*S*)-enantiomer is quite expensive, while both (*R*)- and (*S*)-**1** are readily available[1,36] and easily recoverable, we decided to study the Diels–Alder reactions of esters derived from these chiral auxiliaries, not only with acrylic acid **3**, but also with other acids such as methacrylic, *trans*-crotonic and *trans*-cinnamic acids (**16**, **23**, and **24**, respectively) and different dienes such as cyclopentadiene **5**, isoprene **8**, 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene **9** and anthracene **10**.

2. Results and discussion

Esters derived from (*R*)-, (*S*)- or (±)-**1** and the acids **3**, **16**, **23** and **24** were easily obtained in moderate yields (60, 60, 71 and 92%, respectively) by reaction of the corresponding alcohol and the acid with dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 in the presence of a catalytic amount (5% molar) of 4-(dimethylamino)pyridine (DMAP). The acrylic ester (*S*)-**4** was prepared in an improved way (97% yield) by reaction of (*S*)-**1** with acryloyl chloride **2** and Et_3N in CH_2Cl_2 (Scheme 1).

Dienes were all commercially available except **9** which was prepared as described.[37] According to previous work with D-pantolactone acrylates,[11] the Diels–Alder reactions were carried out under $TiCl_4$ catalysis. The formation of double-coordinated complexes between $TiCl_4$ and the dienophiles derived from D-pantolactone seems to play an important role in connection with the high *facial*-diastereoselectivity of these Diels–Alder reactions, cycloaddition taking place preferentially by the *Re*-face of the acrylate Cα carbon atom. Under similar reaction conditions, other Lewis acid catalysts, such as Et_2AlCl, unable to form double-coordinated complexes with the dienophile, give cycloadducts with very poor *facial*-diastereoselectivities.[11]

Many reactions were first studied by using the racemic dienophiles, and then carried out with one or the other enantiopure reagent. The crude products were usually purified by column chromatography, which may cause some diastereomer enrichment, and the analytical samples of the solid compounds were obtained by recrystallization from the appropriate solvent, thus obtaining the main diastereomer in pure form. The pure or enriched samples of the cycloadducts were hydrolyzed under non-epimerizing conditions,[11] by reaction with $LiOH \cdot H_2O$ in a mixture of THF and water to give the corresponding enantiopure or enantioenriched acids. The absolute configuration of the known acids allowed us to establish the absolute configuration of the corresponding intermediate esters. In two cases, where the acid had not been previously described or its absolute configuration had not been fully established, the relative configuration of the Diels–Alder adducts was established by X-ray diffraction analysis, and their



Scheme 1. *Endo*- and/or *facial*-diastereoselective Diels–Alder reactions of acrylates (*R*)- or (*S*)-**4** with dienes **5**, **8** and **10**

absolute configuration deduced from the knowledge of the absolute configuration of the starting chiral auxiliary.

Acrylate ester (*R*)-**4** reacted with cyclopentadiene in the presence of 0.68 equiv. of $TiCl_4$ at low temperature (−55 to −20°C) to give the *endo*-diastereomer (1*R*,2*R*,3′*R*,4*R*)-**6** in 96% yield of recrystallized product, as the only detectable diastereomer by ^1H and ^{13}C NMR spectroscopy (Scheme 1). LiOH-hydrolysis of this product at room temperature for 26 h gave acid (1*R*,2*R*,4*R*)-**7** (96% yield) whose specific rotation, determined under the described conditions (see the Experimental section), allowed us to establish an o.p. of 97%, in good agreement with the results described for the acrylate of D-pantolactone,[11] taking into account the errors associated with the determination of diastereomeric excesses by NMR spectroscopy and o.p.'s from specific rotations. Similarly, from (*S*)-**4**, (1*S*,2*S*,3′*S*,4*S*)-**6** was obtained in 92% yield, from which acid (1*S*,2*S*,4*S*)-**7** (95% o.p.) was obtained.

Reaction of (*S*)-**4** with isoprene **8** in the presence of 0.50 equiv. of $TiCl_4$ at a temperature from −20 to 10°C for 15 h gave, in 90% yield, an oily product which consisted mainly of the *para*-adduct (1*R*,3′*S*)-**11**. Minor signals in the ^1H and ^{13}C NMR spectra could be attributable to the other *para*-adduct. LiOH-hydrolysis of this product, under similar conditions to that used before, gave acid (*R*)-**14** in 95% yield, whose specific rotation determined under similar conditions to that described (see the Experimental section) allowed us to establish an o.p. of 88%. This result is in reasonable agreement with that described for the related reaction of isoprene and the acrylate of D-pantolactone,[11] where the *para*-adduct was obtained with 94% d.e.

From a reaction of (*S*)-**4** and diene **9** under similar conditions, no cycloadduct was isolated. The

dienophile was mainly recovered while **9** was not, probably because of its instability towards $TiCl_4$. For this reason, the reaction of this diene with the rest of the dienophiles was not attempted.

Reaction of (*S*)-**4** with anthracene **10** required more forcing conditions (18 h at room temperature and 2 equiv. of $TiCl_4$), giving the cycloadduct (11*R*,3′*S*)-**13** in 87% yield of chromatographed product and 93% d.e. by ^{1}H NMR spectroscopy. From this reaction, only two diastereomers are possible due to *facial*-diastereoselectivity since no *endo*-/*exo*-diastereoselectivity is possible for this diene. A reaction of (±)-**4** and **10** carried out in toluene under $AlCl_3$ catalysis required prolonged reflux and gave a mixture of two racemic pairs in an approximate ratio of 3:4, the minor pair corresponding to the main diastereomer in the $TiCl_4$-catalyzed reaction. The signals of the methyl groups in both diastereomers appeared perfectly separated [1.14 and 1.17 ppm for (11*R*,3′*S*)-**13** and 0.90 and 1.10 ppm for (11*S*,3′*S*)-**13**], which allowed us to easily establish the d.e. of the obtained cycloadduct. Recrystallization of the chromatographed product derived from (*S*)-**4** and **10** gave crystalline pure (11*R*,3′*S*)-**13**. LiOH-hydrolysis of this compound gave the corresponding acid, (*R*)-**15**, as a solid in 99% yield. This is a new compound, although its enantiomer had been previously prepared by a similar procedure using the acrylate of D-pantolactone.[13] The specific rotation of (*R*)-**15** was slightly greater in absolute value and of opposite sign to that previously described for its enantiomer. Since the proposed configuration for (*S*)-**15** seems to come from the *facial*-diastereoselectivity observed in the Diels–Alder reactions of D-pantolactone acrylate catalyzed by $TiCl_4$, and to secure this assignment, we carried out an X-ray diffraction analysis of the cycloadduct obtained from (*S*)-**4** and anthracene (Fig. 1) which allowed us to establish its absolute configuration as (11*R*,3′*S*)-**13**, taking into account the (*S*)-configuration of the starting chiral auxiliary, in accord with the expected *facial*-diastereoselectivity, i.e. addition of the diene to the *Re* face of the Cα carbon atom of the acrylate derived from D-pantolactone[13] or (*R*)-**1** and vice versa.

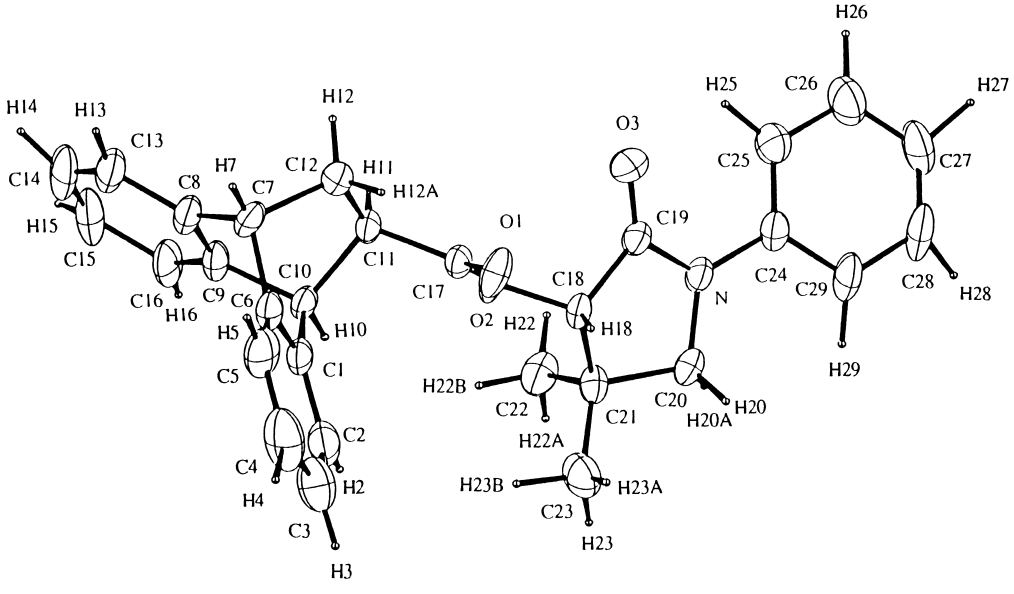
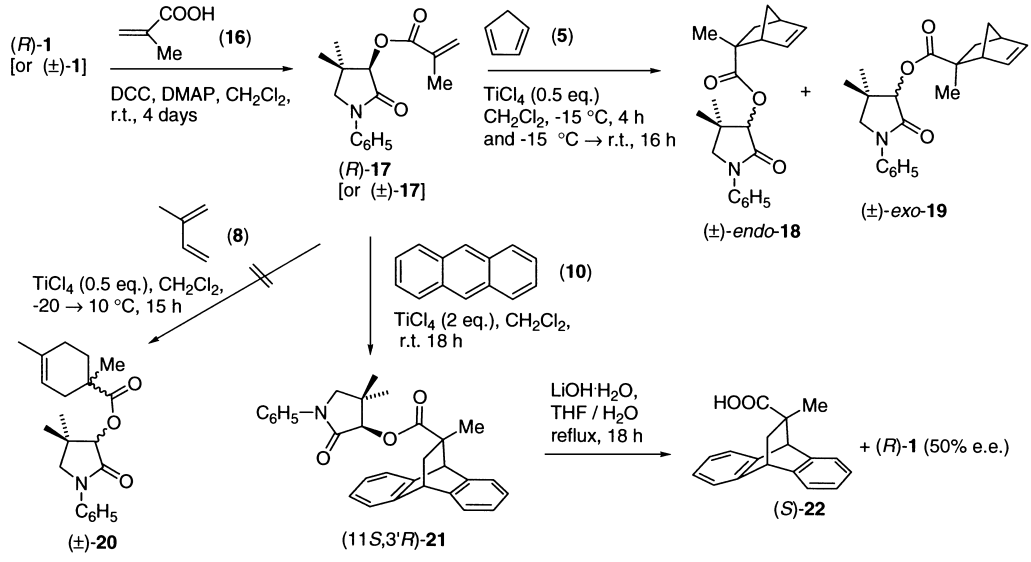


Figure 1. Perspective drawing (ORTEP) of (11*R*,3′*S*)-**13**

Methacrylate (±)-**17** reacted with cyclopentadiene under somewhat more drastic conditions than those used with acrylate **4** to give an essentially 1:1 mixture of *endo*- and *exo*-diastereomers [(±)-*endo*-**18** and (±)-*exo*-**19**] (Scheme 2). Characteristic of (±)-*exo*-**19** are *exo*-3-H (δ=2.55 ppm, dd, $J_{exo\text{-}3H/endo\text{-}3H}$=12.0 Hz, $J_{exo\text{-}3H/4H}$=4.0 Hz) and *endo*-3-H (δ=0.92 ppm, d, $J_{exo\text{-}3H/endo\text{-}3H}$=12.0 Hz) which compare very well with the published data for the corresponding acid[38] [*exo*-3-H (δ=2.46 ppm, dd, $J_{exo\text{-}3H/endo\text{-}3H}$=12.1 Hz,

$J_{exo\text{-}3H/4H}$=3.9 Hz) and *endo*-3-H (δ=0.88 ppm, d, $J_{exo\text{-}3H/endo\text{-}3H}$=12.1 Hz)]. Similarly, in the case of (±)-*endo*-**18**, *exo*-3-H (δ=2.00 ppm, dd, $J_{exo\text{-}3H/endo\text{-}3H}$=12.0 Hz, $J_{exo\text{-}3H/4H}$=3.0 Hz) and *endo*-3-H (δ=1.50 ppm, d, $J_{exo\text{-}3H/endo\text{-}3H}$=12.0 Hz) compare well with the published data for the corresponding acid[38] [*exo*-3-H (δ=1.88 ppm, dd, $J_{exo\text{-}3H/endo\text{-}3H}$=12.0 Hz, $J_{exo\text{-}3H/4H}$=2.6 Hz) and *endo*-3-H (δ=1.15–1.46 ppm, d, $J_{exo\text{-}3H/endo\text{-}3H}$=12.0 Hz)]. The lack of *endo*-/*exo*-diastereoselectivity of the above reaction led us to discard any attempt on the corresponding reaction with (*R*)- or (*S*)-**17** to establish the *facial*-diastereoselectivity.



Scheme 2. *Facial*-diastereoselective Diels–Alder reaction of methacrylate (*R*)-**4** with anthracene

Under similar reaction conditions to that used above, methacrylate (±)-**17** failed to react with isoprene. However, (*R*)-**17** was able to react with anthracene to give the corresponding adduct with high *facial*-diastereoselectivity. Under the optimum conditions assayed (CH_2Cl_2, 2 equiv. $TiCl_4$, room temperature, 18 h), (11*S*,3′*R*)-**21** was obtained in 97% yield as the only diastereomer detectable by ^1H and ^{13}C NMR (d.e. >98%). Compound (±)-**17** was not able to react with anthracene under $AlCl_3$ catalysis, and thus, we do not know the characteristic signals in ^1H and ^{13}C NMR of (11*R*,3′*R*)-**21**. The relative configuration of the new compound (11*S*,3′*R*)-**21** was obtained by X-ray diffraction analysis (Fig. 2) of a monocrystal obtained by careful crystallization of the product from methanol. From this relative configuration and knowing the absolute configuration of the starting chiral auxiliary, the absolute configuration of this cycloadduct was deduced.

The *facial*-diastereoselectivity observed in the reaction of methacrylate (*R*)-**17** and anthracene is the same observed in the reactions with acrylate (*S*)-**4**: from (*R*)-**17**, (11*S*,3′*R*)-**21** was obtained while from (*S*)-**4**, (11*R*,3′*S*)-**13** had been obtained. However, the *facial*-diastereoselectivity in the Diels–Alder addition to methacrylate esters implies preferential addition by the *Si* face of the Cα carbon atom of (*R*)-**17**, what is apparently contrary to the situation found in the case of the corresponding acrylates. This is due to the presence of the methyl group at position α in methacrylate **17**, which provokes a change in the notation of the enantiotopic faces of this Cα carbon atom: the *Re* face of acrylate esters become the *Si* face in methacrylate esters and vice versa.

As expected, hydrolysis of the more hindered ester (11*S*,3′*R*)-**21** required more drastic conditions (LiOH, THF/H_2O, 18 h under reflux) than those generally used to hydrolyze the acrylate cycloadducts. Under these conditions, epimerization of the chiral auxiliary was important, (*R*)-**1** being recovered in

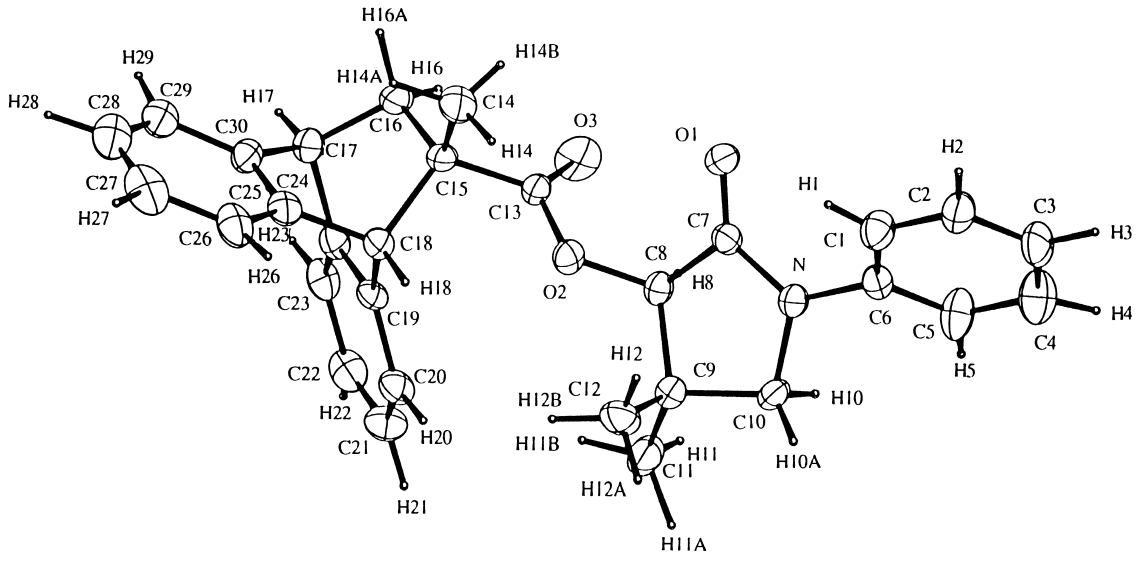
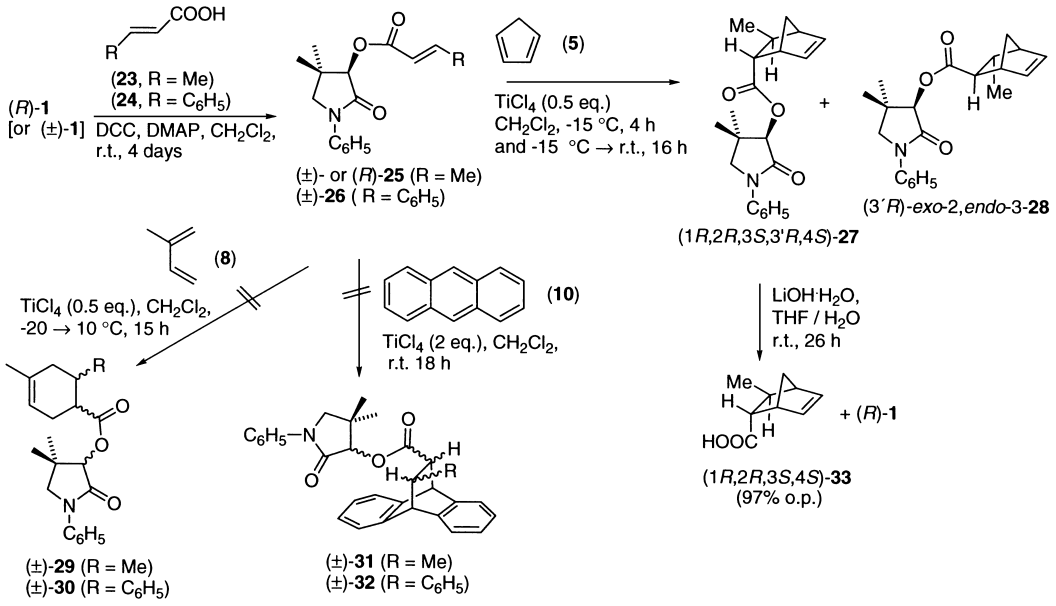


Figure 2. Perspective drawing (ORTEP) of (11*S*,3′*R*)-**21**

96% yield but only 50% e.e. (chiral HPLC).[1] Since the obtained acid (*S*)-**22** cannot epimerize under the basic hydrolysis conditions (except via a retro-Diels–Alder/Diels–Alder reaction), the e.e. of the new acid (*S*)-**22** must be the same as the d.e. of ester (11*S*,3′*R*)-**21**, i.e.: >98%.

The *trans*-cinnamate (±)-**26** failed to react with isoprene, anthracene and cyclopentadiene, and the *trans*-crotonate (±)-**25** failed to react with isoprene and anthracene, although (*R*)-**25** was reacted smoothly with cyclopentadiene to give, after column chromatography, the *endo*-adduct (1*R*,2*R*,3*S*,3′*R*,4*S*)-**27** (71% yield) and an *exo*-adduct, (3′*R*)-*exo*-2-*endo*-3-**28** (2% yield). Both products showed to be only one diastereomer by ^{1}H and ^{13}C NMR spectroscopy, whose d.e.s must be >98% (Scheme 3). The absolute configuration of (1*R*,2*R*,3*S*,3′*R*,4*S*)-**27** was deduced after LiOH-hydrolysis under the standard conditions (LiOH, THF/H_2O, room temperature) to the known acid (1*R*,2*R*,3*S*,4*S*)-**33**.[39] The o.p. of the oily acid was shown to be 97%, in good agreement with the d.e. of the corresponding ester. The absolute configuration of (3′*R*)-*exo*-2-*endo*-3-**28** could not be deduced due to the small amount of product available, which precluded its hydrolysis, but the *exo*-2-*endo*-3 nature of the adduct could be established by comparison of its ^{13}C NMR spectrum with the data reported for the corresponding *exo*-2-*endo*-3-acid.[40]

In conclusion, acrylic esters derived from the chiral auxiliaries (*R*)- or (*S*)-**1**, react, as expected, with different dienes (cyclopentadiene, isoprene and anthracene) under $TiCl_4$ catalysis, with high *facial*- and *endo*-selectivity. However, methacrylic esters derived from these chiral auxiliaries fail to react under these conditions with poor reactive dienes, such as isoprene, react with cyclopentadiene without *endo*-selectivity, but react with anthracene with high *facial*-selectivity. The less reactive *trans*-crotonic esters react only with the more reactive cyclopentadiene with high *facial*- and *endo*-selectivity, while the still less reactive *trans*-cinnamic esters fail to react with any of the studied dienes. Except for the cycloadduct (11*S*,3′*R*)-**21**, derived from methacrylate (*R*)-**17**, the chiral auxiliary was always recovered in high yield without loss of enantiomeric purity, after controlled LiOH-hydrolysis of the Diels–Alder adducts. The present work expands the usefulness of the chiral auxiliaries (*R*)- and (*S*)-**1**, for which a simpler synthesis will soon be submitted for publication.



Scheme 3. *Endo*- and *facial*-diastereoselective Diels–Alder reaction of *trans*-crotonate (*R*)-**25** with cyclopentadiene

3. Experimental

Melting points were determined on a MFB 595010 M Gallenkamp melting point apparatus. ^{1}H NMR spectra (500 MHz) were performed on a Varian VXR 500 spectrometer and 300 MHz ^{1}H and 75.4 MHz ^{13}C NMR spectra on a Varian Gemini 300. Except where otherwise stated, ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 75.4 MHz, always in $CDCl_3$. COSY ^{1}H/^{1}H experiments were carried out by using standard procedures while for the COSY ^{1}H/^{13}C experiments, the HMQC sequence with an indirect detection probe was used. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane. IR spectra were recorded on an FT/IR Perkin–Elmer spectrometer, model 1600. Optical rotations were measured on a Perkin–Elmer model 241 polarimeter. Solvents were of analytical grade. Elemental analyses were carried out at the Microanalysis Service of the Centro de Investigación y Desarrollo (C.I.D.), Barcelona, Spain.

*3.1. General procedure for the preparation of esters **4**, **17**, **25** and **26***

A mixture of the acids **3**, **16**, **23** or **24** (1.00 mmol), (*R*)- or (*S*)-**1** (1.00 mmol), DCC (1.00 mmol) and DMAP (0.05 mmol) in anhydrous CH_2Cl_2 (10 ml) was stirred at room temperature under an argon atmosphere for 4 days. The mixture was filtered, the filtrate was washed with saturated aqueous solution of citric acid (3×10 ml) and saturated aqueous $NaHCO_3$ (3×10 ml), dried with anh. Na_2SO_4 and concentrated in vacuo. The residue was submitted to column chromatography [silica gel (20 g), CH_2Cl_2] to give pure esters **4**, **17**, **25** or **26**.

*3.1.1. (*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl acrylate (*R*)-**4***

Following the above general procedure, from **3** (1.00 g, 14.0 mmol), (*R*)-**1** (2.87 g, 14.0 mmol), (*R*)-**4** (1.60 g, 44% yield) was obtained as a solid, m.p. 98–100°C (ethanol), $[\alpha]_D^{20}$=+23.9 (*c* 1.00, $CHCl_3$), IR (KBr) ν: 1733 and 1703 (C=O st), 1627 (C=C st) cm^{-1}. $C_{15}H_{17}NO_3$ (259.32): calcd: C, 69.48%; H, 6.61%; N, 5.40%. Found: C, 69.50%; H, 6.63%; N, 5.49%. ^{1}H NMR (300 MHz) δ: 1.15 (s, 3H, 4α-

CH_3), 1.31 (s, 3H, 4β-CH_3), 3.53 (d, *J*=9.6 Hz, 1H, 5α-H), 3.63 (d, *J*=9.6 Hz, 1H, 5β-H), 5.48 (s, 1H, 3-H), 5.94 (dd, *J*=10.4 Hz, *J′*=1.2 Hz, 1H, β-H*trans*), 6.26 (dd, *J*=17.3 Hz, *J′*=10.4 Hz, 1H, α-H), 6.54 (dd, *J*=17.3 Hz, *J′*=1.2 Hz, 1H, β-H*cis*), 7.17 (broad t, *J*=7.4 Hz, 1H, H*para*), 7.38 (m, 2H, H*meta*), 7.63 (broad d, *J*=7.8 Hz, 2H, H*ortho*); ^{13}C NMR δ: 21.1 (CH_3, 4α-CH_3), 24.8 (CH_3, 4β-CH_3), 37.5 (C, C4), 57.7 (CH_2, C5), 78.3 (CH, C3), 119.4 (CH, C*ortho*), 124.9 (CH, C*para*), 127.5 (CH, Cα), 128.9 (CH, C*meta*), 132.1 (CH_2, Cβ), 139.0 (C, C*ipso*), 165.3 (C, COO), 168.8 (C, C2).

*3.1.2. (*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl acrylate (*S*)-**4***

Following the above general procedure, from **3** (1.00 g, 14.0 mmol), (*S*)-**1** (2.87 g, 14.0 mmol), (*S*)-**4** (1.54 g, 43% yield) was obtained as a solid, m.p. 97–99°C (ethanol), $[\alpha]_D^{20}$=−24.3 (*c* 1.00, $CHCl_3$), IR (KBr) ν: 1727 and 1708 (C=O st), 1626 (C=C st) cm^{-1}. $C_{15}H_{17}NO_3$ (259.32): calcd: C, 69.48%; H, 6.61%; N, 5.40%. Found: C, 69.48%; H, 6.60%; N, 5.53%. The NMR data are coincidental with those of its enantiomer.

*3.1.3. (*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl methacrylate (*R*)-**17***

Following the above general procedure, from **16** (0.43 g, 5.00 mmol), (*R*)-**1** (1.03 g, 5.00 mmol), (*R*)-**17** (0.77 g, 60% yield) was obtained as a solid, m.p. 58–60°C (ethanol), $[\alpha]_D^{20}$=+29.6 (*c* 1.04, $CHCl_3$), IR (KBr) ν: 1760 and 1712 (C=O st), 1597 (C=C st) cm^{-1}. $C_{16}H_{19}NO_3$ (273.35): calcd: C, 70.31%; H, 7.01%; N, 5.12%. Found: C, 70.24%; H, 7.04%; N, 5.19%. ^{1}H NMR δ: 1.18 (s, 3H, 4α-CH_3), 1.32 (s, 3H, 4β-CH_3), 2.04 (s, 3H, α-CH_3), 3.54 (d, *J*=9.6 Hz, 1H, 5α-H), 3.64 (d, *J*=9.6 Hz, 1H, 5β-H), 5.49 (s, 1H, 3-H), 5.69 (broad s, 1H, β-H*trans*), 6.28 (broad s, 1H, β-H*cis*), 7.18 (broad t, *J*=7.4 Hz, 1H, H*para*), 7.39 (m, 2H, H*meta*), 7.66 (broad d, *J*=8.5 Hz, 2H, H*ortho*). ^{13}C NMR δ: 18.3 (CH_3, α-CH_3), 21.1 (CH_3, 4-αCH_3), 24.7 (CH_3, 4-βCH_3), 37.4 (C, C4), 57.5 (CH_2, C5), 78.2 (CH, C3), 119.3 (CH, C*ortho*), 124.7 (CH, C*para*), 126.8 (CH_2, Cβ), 128.8 (CH, C*meta*), 135.2 (C, Cα), 139.0 (C, C*ipso*), 166.4 (C, COO), 168.8 (C, C2).

*3.1.4. (*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl crotonate (*R*)-**25***

Following the above general procedure, from **23** (1.00 g, 12.0 mmol), (*R*)-**1** (2.46 g, 12.0 mmol), (*R*)-**25** (1.50 g, 46% yield) was obtained as a solid, m.p. 97–99°C (ethanol), $[\alpha]_D^{20}$=+31.1 (*c* 1.84, $CHCl_3$), IR (KBr) ν: 1719 (C=O st), 1634 (C=C st) cm^{-1}. $C_{16}H_{19}NO_3$ (273.35): calcd: C, 70.31%; H, 7.01%; N, 5.12%. Found: C, 70.22%; H, 7.13%; N, 5.23%. ^{1}H NMR (300 MHz) δ: 1.14 (s, 3H, 4α-CH_3), 1.30 (s, 3H, 4β-CH_3), 1.92 (dd, *J*=6.9 Hz, *J′*=1.7 Hz, 3H, β-CH_3), 3.52 (d, *J*=9.5 Hz, 1H, 5α-H), 3.63 (d, *J*=9.5 Hz, 1H, 5β-H), 5.46 (s, 1H, 3-H), 5.99 (dq, *J*=15.6 Hz, *J′*=1.7 Hz, 1H, α-H), 7.12 (dq, *J*=15.6 Hz, *J′*=6.9 Hz, 1H, β-H), 7.16 (broad t, *J*=7.5 Hz, 1H, H*para*), 7.38 (m, 2H, H*meta*), 7.64 (dm, *J*=7.8 Hz, 2H, H*ortho*). ^{13}C NMR δ: 18.1 (CH_3, β-CH_3), 21.1 (CH_3, 4α-CH_3), 24.9 (CH_3, 4β-CH_3), 37.5 (C, C4), 57.7 (CH_2, C5), 77.9 (CH, C3), 119.4 (CH, C*ortho*), 121.8 (C, Cα), 124.8 (CH, C*para*), 128.9 (CH, C*meta*), 139.1 (C, C*ipso*), 146.4 (CH, Cβ), 165.5 (C, COO), 169.1 (C, C2).

3.1.5. rac-*4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl cinnamate* rac-**26**

Following the above general procedure, from **24** (3.70 g, 25.0 mmol), *rac*-**1** (5.12 g, 25.0 mmol), *rac*-**26** (7.68 g, 92% yield) was obtained as a solid, m.p. 105–106°C (ethanol).[6]

*3.2. (*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl acrylate (*S*)-**4***

To a cold (−20°C) solution of (*S*)-**1** (1.02 g, 4.98 mmol) and triethylamine (14 ml, 9.95 mmol) in anhydrous CH_2Cl_2 (25 ml), acryloyl chloride (**2**, 0.50 ml, 5.98 mmol) was added. After 10 min, the

mixture was washed with 1 N HCl (3×25 ml) and saturated aqueous $NaHCO_3$ (3×25 ml). The organic layer was dried with anh. Na_2SO_4 and concentrated in vacuo to give solid (*S*)-**4** (1.25 g, 97% yield).

*3.3. General procedure for the Diels–Alder reactions of esters **4**, **17**, **25** or **26** and cyclopentadiene, isoprene or anthracene*

A solution of $TiCl_4$ (0.50, 0.75 or 1.00 mmol) in anhydrous CH_2Cl_2 (2 ml) was added to a solution of ester **4**, **17**, **25** or **26** (1.00 mmol) in anhydrous CH_2Cl_2 (3 ml). The mixture was stirred at −55, −20, −15°C or at room temperature for 15 min. Then, a solution of the diene (1.00 or 2.40 mmol) in anhydrous CH_2Cl_2 (3 ml) was added and it was stirred for the specified time at the indicated temperature. Powdered Na_2CO_3 or a small amount of water was added to destroy the $TiCl_4$ complexes, the mixture was filtered and the filtrate was dried with anh. Na_2SO_4. The filtrate was concentrated in vacuo and the residue was submitted to column chromatography [silica gel (20 g), CH_2Cl_2 or ethyl acetate/hexane] and/or to crystallization to give esters **6**, **11**, **13**, **21** or **27**.

*3.3.1. (1*R,*2*R,*3′*R,*4*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl bicyclo[2.2.1]hept-5-ene-2-carboxylate (1*R,*2*R,*3′*R,*4*R*)-**6***

Following the above general procedure, from (*R*)-**4** (0.69 g, 2.66 mmol), $TiCl_4$ (0.2 ml, 1.8 mmol) and cyclopentadiene (0.35 g, 5.32 mmol), after 4 h at −55°C and then 16 h more at a temperature from −55 to −20°C, (1*R*,2*R*,3′*R*,4*R*)-**6** (0.83 g, 96% yield) was obtained as a solid, after crystallization from ethyl acetate:hexane (1:1, 1 ml), m.p. 139–141°C (ethyl acetate–hexane), $[\alpha]_D^{20}$=−41.2 (*c* 1.00, $CHCl_3$), IR (KBr) ν: 1744 and 1710 (C=O st) cm^{-1}. $C_{20}H_{23}NO_3$ (325.42): calcd: C, 73.82%; H, 7.13%; N, 4.30%. Found: C, 73.90%; H, 7.12%; N, 4.27%. ^{1}H NMR δ: 1.15 (s, 3H, 4′α-CH_3), 1.25 (s, 3H, 4′β-CH_3), 1.31 (broad d, *J*=8.0 Hz, 1H, 7-H*syn*), 1.46 (pseudo dq, *J*=8.0 Hz, *J′*=2.0 Hz, 1H, 7-H*anti*), 1.50 (ddd, *J*=12.0 Hz, *J′*=4.0 Hz, *J″*=3.0 Hz, 1H, 3-H*endo*), 1.94 (ddd, *J*=12.0 Hz, *J′*=9.5 Hz, *J″*=4.0 Hz, 1H, 3-H*exo*), 2.93 (broad s, 1H, 4-H), 3.18 (dt, *J*=9.5 Hz, *J′*=4.0 Hz, 1H, 2-H*exo*), 3.28 (broad s, 1H, 1-H), 3.49 (d, *J*=9.5 Hz, 1H, 5′α-H), 3.59 (d, *J*=9.5 Hz, 1H, 5′β-H), 5.35 (s, 1H, 3′-H), 5.93 (dd, *J*=6.0 Hz, *J′*=3.0 Hz, 1H, 6-H), 6.25 (dd, *J*=6.0 Hz, *J′*=3.0 Hz, 1H, 5-H), 7.15 (broad t, *J*=7.5 Hz, 1H, H*para*), 7.36 (m, 2H, H*meta*), 7.60 (dm, *J*=8.0 Hz, 2H, H*ortho*). ^{13}C NMR δ: 21.3 (CH_3, 4′α-CH_3), 24.8 (CH_3, 4′β-CH_3), 29.0 (CH_2, C3), 37.4 (C, C4′), 42.5 (CH, C4), 43.1 (CH, C2), 46.1 (CH, C1), 49.9 (CH_2, C7), 57.6 (CH_2, C5′), 77.8 (CH, C3′), 119.4 (CH, C*ortho*), 124.8 (CH, C*para*), 128.9 (CH, C*meta*), 131.6 (CH, C6), 138.4 (CH, C5), 139.1 (C, C*ipso*), 169.1 (C, C2′), 173.9 (C, COO).

*3.3.2. (1*S,*2*S,*3′*S,*4*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl bicyclo[2.2.1]hept-5-ene-2-carboxylate (1*S,*2*S,*3′*S,*4*S*)-**6***

Following the above general procedure, from (*S*)-**4** (0.54 g, 2.08 mmol), $TiCl_4$ (0.12 ml, 1.09 mmol) and cyclopentadiene (0.38 g, 4.16 mmol), after 4 h at −55°C and then 16 h more at a temperature from −55 to −20°C, (1*S*,2*S*,3′*S*,4*S*)-**6** (0.67 g, 92% yield) was obtained as a solid, after crystallization from ethyl acetate:hexane (1:1, 1 ml), m.p. 140–141°C (ethyl acetate–hexane), $[\alpha]_D^{20}$=+39.3 (*c* 1.00, $CHCl_3$), IR (KBr) ν: 1744 and 1716 (C=O st) cm^{-1}. $C_{20}H_{23}NO_3$ (325.42): calcd: C, 73.82%; H, 7.13%; N, 4.30%. Found: C, 73.74%; H, 7.07%; N, 4.47%. The NMR data are coincidental with those of its enantiomer.

*3.3.3. (1*R,*3′*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 4-methylcyclohex-3-enecarboxylate (1*R,*3′*S*)-**11***

Following the above general procedure, from (*S*)-**4** (105 mg, 0.41 mmol), $TiCl_4$ (0.02 ml, 0.2 mmol) and isoprene (0.08 ml, 0.82 mmol), after 15 min at −20°C and then 15 h more at a temperature from

−20 to 10°C, (1*R*,3′*S*)-**11** (119 mg, 90% yield) was obtained as an oil, after column chromatography [silica gel (5 g), CH_2Cl_2], $[\alpha]_D^{20}$=+6.7 (*c* 0.85, $CHCl_3$), IR (NaCl) ν: 1740 and 1716 (C=O st) cm^{-1}. $C_{20}H_{25}NO_3$ (327.44): calcd: C, 73.36%; H, 7.70%; N, 4.28%. Found: C, 73.18%; H, 7.80%; N, 4.23%. ^{1}H NMR δ: 1.11 (s, 3H, 4′α-CH_3), 1.27 (s, 3H, 4′β-CH_3), 1.65 (d, *J*=1.5 Hz, 3H, 4-CH_3), 1.81 (m, 1H, 6α-H), 2.02 (complex signal, 2H, 5α-H and 5β-H), 2.09 (m, 1H, 6β-H), 2.30 (complex signal, 2H, 2α-H and 2β-H), 2.69 (dtd, *J*=11.0 Hz, *J*′=7.5 Hz, *J*′′=3.0 Hz, 1H, 1-H), 3.50 (d, *J*=9.5 Hz, 5′α-H), 3.60 (d, *J*=9.5 Hz, 1H, 5′β-H), 5.37 (m, 1H, 3-H), 5.40 (s, 1H, 3′-H), 7.15 (tm, *J*=7.5 Hz, 1H, H*para*), 7.35 (dd, *J*=8.5 Hz, *J*′=7.5 Hz, 2H, H*meta*), 7.61 (dm, *J*=8.5 Hz, 2H, H*ortho*). ^{13}C NMR δ: 21.1 (CH_3, 4′α-CH_3), 23.5 (CH_3, 4-CH_3), 24.8 (CH_3, 4′β-CH_3), 25.4 (CH_2, C6), 27.8 (CH_2, C2), 29.0 (CH_2, C5), 37.4 (C, C4′), 39.1 (CH, C1), 57.7 (CH_2, C5′), 77.8 (CH, C3′), 118.9 (CH, C3), 119.4 (CH, C*ortho*), 124.8 (CH, C*para*), 128.9 (CH, C*meta*), 134.0 (C, C4), 139.1 (C, C*ipso*), 169.1 (C, C2′), 175.2 (C, COO).

*3.3.4. (11*R,*3′*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 9,10-dihydro-9,10-ethanoanthracene-11-carboxylate (11*R,*3′*S*)-**13***

Following the above general procedure, from (*S*)-**4** (0.80 g, 3.09 mmol), $TiCl_4$ (0.68 ml, 6.18 mmol) and anthracene (0.55 g, 3.09 mmol) at room temperature for 18 h, (11*R*,3′*S*)-**13** (1.17 g, 87% yield) was obtained as a solid, after column chromatography [silica gel (60 g), CH_2Cl_2], m.p. 175–177°C (methanol), $[\alpha]_D^{20}$=+5.8 (*c* 1.06, $CHCl_3$), IR (KBr) ν: 1749 and 1707 (C=O st) cm^{-1}. $C_{29}H_{27}NO_3$ (437.56): calcd: C, 79.61%; H, 6.22%; N, 3.20%. Found: C, 79.45%; H, 6.22%; N, 3.21%. ^{1}H NMR δ: 1.14 (s, 3H, 4′α-CH_3), 1.17 (s, 3H, 4′β-CH_3), 2.02 (ddd, *J*=12.5 Hz, *J*′=10.5 Hz, *J*′′=2.5 Hz, 1H, 12-H*anti*), 2.18 (ddd, *J*=12.5 Hz, *J*′=4.5 Hz, *J*′′=2.5 Hz, 1H, 12-H*syn*), 3.05 (ddd, *J*=10.5 Hz, *J*′=5.0 Hz, *J*′′=2.5 Hz, 1H, 11-H), 3.43 (d, *J*=9.5 Hz, 1H, 5′α-H), 3.51 (d, *J*=9.5 Hz, 1H, 5′β-H), 4.30 (t, *J*=2.5 Hz, 1H, 9-H), 4.65 (d, *J*=3.0 Hz, 1H, 10-H), 5.23 (s, 1H, 3′-H), 6.99 (td, *J*=7.0 Hz, *J*′=1.0 Hz, 1H), 7.01-7.07 (complex signal, 4H) (2-H, 3-H, 6-H and 7-H), 7.10 (tm, *J*=7.0 Hz, 1H, H*para N*-phenyl), 7.17–7.26 (complex signal, 4H) (1-H, 4-H, 5-H and 8-H), 7.31 (dd, *J*=8.5 Hz, *J*′=7.0 Hz, 2H, H*meta N*-phenyl), 7.55 (dm, *J*=8.5 Hz, 2H, H*ortho N*-phenyl). ^{13}C NMR δ: 21.3 (CH_3, 4′α-CH_3), 24.7 (CH_3, 4′β-CH_3), 31.0 (CH_2, C12), 37.4 (C, C4′), 43.7 (CH, C9), 44.1 (CH, C11), 46.8 (CH, C10), 57.6 (CH_2, C5′), 78.3 (CH, C3′), 119.4 (CH, C*ortho N*-phenyl), 123.4 (CH), 123.5 (CH), 123.6 (CH), 124.7 (CH), 125.5 (CH), 125.7 (CH), 126.2 (CH) and 126.4 (CH) (Ar-CH anthracene), 124.9 (CH, C*para N*-phenyl), 128.9 (CH, C*meta N*-phenyl), 139.0 (C, C*ipso N*-phenyl), 139.6 (C), 142.3 (C) and 143.8 (2 C) (Ar-C anthracene), 168.8 (C, C2′), 172.8 (C, COO).

*3.3.5. Mixture of (±)-*endo- *and (±)-*exo-*4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-methylbicyclo[2.2.1]hept-5-ene-2-carboxylate (±)-*endo-***18** *and (±)-*exo-***19***

Following the above general procedure, from *rac*-**17** (0.41 g, 1.50 mmol), $TiCl_4$ (0.08 ml, 0.75 mmol) and cyclopentadiene (0.20 g, 3.5 mmol), after 4 h at −15°C and then 16 h more at a temperature from −15°C to room temperature, a solid mixture of (±)-*endo*-**18** and (±)-*exo*-**19** in the approximate ratio of 1:1 (0.37 g, 73% yield) was obtained, after column chromatography [silica gel (40 g), hexane:ethyl acetate], m.p. 107–109°C (ethyl acetate–hexane).

*3.3.6. (11*S,*3′*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 9,10-dihydro-11-methyl-9,10-ethanoanthracene-11-carboxylate (11*S,*3′*R*)-**21***

Following the above general procedure, from (*R*)-**17** (0.68 g, 2.49 mmol), $TiCl_4$ (0.60 ml, 4.98 mmol) and anthracene (0.45 g, 2.49 mmol) at room temperature for 18 h, (11*S*,3′*R*)-**21** (1.09 g, 96% yield) was obtained as a solid, after column chromatography [silica gel (50 g), CH_2Cl_2], m.p. 214–216°C (methanol), $[\alpha]_D^{20}$=−10.5 (*c* 1.06, $CHCl_3$), IR (KBr) ν: 1740 and 1710 (C=O st) cm^{-1}. $C_{30}H_{29}NO_3$

(451.59): calcd: C, 79.79%; H, 6.48%; N, 3.10%. Found: C, 79.78%; H, 6.52%; N, 3.05%. ^{1}H NMR δ: 1.21 (s, 3H, 11-CH_3), 1.24 (s, 3H, 4′β-CH_3), 1.26 (s, 3H, 4′α-CH_3), 1.50 (dd, *J*=12.5 Hz, *J′*=2.5 Hz, 1H, 12-H*anti*), 2.78 (dd, *J*=12.5 Hz, *J′*=3.0 Hz, 1H, 12-H*syn*), 3.50 (d, *J*=9.5 Hz, 1H, 5′α-H), 3.55 (d, *J*=9.5 Hz, 1H, 5′β-H), 4.27 (t, *J*=3.0 Hz, 1H, 9-H), 4.43 (s, 1H, 10-H), 5.23 (s, 1H, 3′-H), 7.02 (td, *J*=7.5 Hz, *J′*=1.5 Hz, 1H), 7.06 (td, *J*=7.0 Hz, *J′*=1.5 Hz, 1H), 7.08–7.12 (complex signal, 4 H) (2-H, 3-H, 6-H and 7-H), 7.14 (tm, *J*=7.5 Hz, 1H, H*para N*-phenyl), 7.23–7.32 (complex signal, 4 H) (1-H, 4-H, 5-H and 8-H), 7.35 (dd, *J*=8.5 Hz, *J′*=7.5 Hz, 2H, H*meta N*-phenyl), 7.60 (dm, *J*=8.5 Hz, 2H, H*ortho N*-phenyl). ^{13}C NMR δ: 21.4 (CH_3, 4′α-CH_3), 24.5 (CH_3, 4′β-CH_3), 27.3 (CH_3, 11-CH_3), 37.3 (C, C4′), 39.1 (CH_2, C12), 44.3 (CH, C9), 48.9 (C, C11), 52.3 (CH, C10), 57.5 (CH_2, C5′), 78.3 (CH, C3′), 119.2 (CH, C*ortho N*-phenyl), 123.1 (CH), 123.6 (CH), 124.7 (2 CH), 125.3 (CH), 125.5 (CH), 125.9 (CH) and 126.3 (2 CH) [Ar-CH anthracene and C*para N*-phenyl (124.7)], 128.9 (CH, C*meta N*-phenyl), 139.1 (C, C*ipso N*-phenyl), 140.5 (C), 141.2 (C), 143.4 (C) and 143.6 (C) (Ar-C anthracene), 168.8 (C, C2′), 175.8 (C, COO).

*3.3.7. (1*R,*2*R,*3*S,*3′*R,*4*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-methylbicyclo[2.2.1]hept-5-ene-2-carboxylate (1*R,*2*R,*3*S,*3′*R,*4*S*)-**27** and (3′*R*)-4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl* endo-*3-methylbicyclo[2.2.1]hept-5-ene*-exo-*2-carboxylate (3′*R*)*-exo-*2*-endo-*3*-**28**

Following the above general procedure, from (*R*)-**25** (1.41 g, 5.15 mmol), $TiCl_4$ (0.30 ml, 2.70 mmol) and cyclopentadiene (0.68 g, 10.3 mmol), after 4 h at −15°C and then 16 h more at a temperature from −15°C to room temperature, (1*R*,2*R*,3*S*,3′*R*,4*S*)-**27** (1.25 g, 71% yield) was obtained as a solid, after column chromatography [silica gel (60 g), hexane/diethylether], m.p. 93–95°C (diethyl ether–hexane). A small amount of a less polar oily adduct, characterized as (3′*R*)-*exo*-2-*endo*-3-**28** (40 mg, 2% yield), was also isolated.

*3.3.7.1. Analytical and spectroscopic data of (1*R,*2*R,*3*S,*3′*R,*4*S*)-**27**.* $[\alpha]_D^{20}$=−43.0 (*c* 2.00, $CHCl_3$), IR (KBr) ν: 1743 and 1718 (C=O st) cm^{-1}. $C_{21}H_{25}NO_3 \cdot 1/4H_2O$ (343.96): calcd: C, 73.33%; H, 7.48%; N, 4.07%. Found: C, 73.50%; H, 7.47%; N, 4.16%. ^{1}H NMR δ: 1.13 (s, 3H, 4′α-CH_3), 1.19 (d, *J*=6.5 Hz, 3H, 3*exo*-CH_3), 1.24 (s, 3H, 4′β-CH_3), 1.45 (pseudo dq, *J*=8.5 Hz, *J′*=1.5 Hz, 1H, 7-H*anti*), 1.57 (broad d, *J*=8.5 Hz, 1H, 7-H*syn*), 1.95 (ddq, *J*=4.5 Hz, *J′*=1.5 Hz, *J″*=7.0 Hz, 1H, 3-H*endo*), 2.48 (broad s, 1H, 4-H), 2.59 (dd, *J*=4.5 Hz, *J′*=4.0 Hz, 1H, 2-H*exo*), 3.19 (broad s, 1H, 1-H), 3.48 (d, *J*=9.5 Hz, 1H, 5′α-H), 3.57 (d, *J*=9.5 Hz, 1H, 5′β-H), 5.33 (s, 1H, 3′-H), 5.98 (dd, *J*=6.0 Hz, J′=3.0 Hz, 1H, 6-H), 6.31 (dd, *J*=6.0 Hz, *J′*=3.0 Hz, 1H, 5-H), 7.14 (broad t, *J*=7.0 Hz, 1H, H*para*), 7.35 (m, 2H, H*meta*), 7.60 (broad d, *J*=8.0 Hz, 2H, H*ortho*). ^{13}C NMR δ: 20.7 (CH_3, 3*exo*-CH_3), 21.2 (CH_3, 4′α-CH_3), 24.7 (CH_3, 4′β-CH_3), 37.3 (C, C4′), 37.4 (CH, C3), 46.1 (CH and CH_2, C1 and C7), 48.7 (CH, C4), 52.0 (CH, C2), 57.4 (CH_2, C5′), 77.6 (CH, C3′), 119.3 (CH, C*ortho*), 124.7 (CH, C*para*), 128.8 (CH, C*meta*), 132.5 (CH, C6), 139.0 (C, C*ipso*), 139.2 (C, C5), 169.0 (C, C2′), 173.6 (C, COO).

*3.3.7.2. Analytical and spectroscopic data of (3′*R*)*-exo-*2*-endo-*3*-**28**.* $[\alpha]_D^{20}$=+6.68 (*c* 2.00, $CHCl_3$), IR (NaCl) ν: 1742 and 1718 (C=O st) cm^{-1}. $C_{21}H_{25}NO_3.1/4H_2O$ (343.96): calcd: C, 73.33%; H, 7.48%; N, 4.07%. Found: C, 73.58%; H, 7.41%; N, 4.09%. ^{1}H NMR (300 MHz) δ: 0.96 (d, *J*=6.9 Hz, 3H, 3-*endo*-CH_3), 1.16 (s, 3H, 4′-αCH_3), 1.31 (s, 3H, 4′-βCH_3), 1.49 (pseudo dq, *J*=8.6 Hz, *J′*=1.7 Hz, 1H, 7-H*anti*), 1.70 (broad d, *J*=8.6 Hz, 1H, 7-H*syn*), 1.85 (dd, *J*=5.0 Hz, *J′*=1.7 Hz, 1H, 2-H*endo*), 2.55 (ddq, *J*=3.4 Hz, *J′*=5.0 Hz, *J″*=6.9 Hz, 1H, 3-H*exo*), 2.75 (broad s, 1H, 4-H), 3.05 (broad s, 1H, 1-H), 3.53 (d, *J*=9.5 Hz, 1H, 5′α-H), 3.63 (d, *J*=9.5 Hz, 1H, 5′β-H), 5.42 (s, 1H, 3′-H), 6.14 (dd, *J*=5.6 Hz, *J′*=3.0 Hz, 1H) and 6.23 (dd, *J*=5.6 Hz, *J′*=3.1 Hz, 1H) (5-H and 6-H), 7.17 (tt, *J*=7.4 Hz, *J′*=1.2 Hz, 1H, H*para*),

7.38 (m, 2H, H*meta*), 7.63 (dm, *J*=7.6 Hz, 2H, H*ortho*). ^{13}C NMR δ: 19.1 (CH_3, 3-*endo*-CH_3), 21.2 (CH_3, 4′α-CH_3), 24.8 (CH_3, 4′β-CH_3), 37.3 (C, C4′), 39.3 (CH, C3), 47.2 (2 CH, C1 and C4), 48.2 (CH_2, C7), 51.2 (CH, C2), 57.7 (CH_2, C5′), 77.9 (CH, C3′), 119.4 (CH, C*ortho*), 124.8 (CH, C*para*), 128.9 (CH, C*meta*), 135.5 (CH) and 136.3 (CH) (C5 and C6), 139.1 (C, C*ipso*), 169.1 (C, C2′), 175.4 (C, COO).

*3.4. General procedure for the hydrolysis of esters **6**, **11**, **13**, **21** and **27***

To a solution of the ester **6**, **11**, **13**, **21** or **27** (1.0 mmol) in a mixture of THF (3.0 ml) and water (2.5 ml), solid $LiOH \cdot H_2O$ (1.5 or 4.5 mmol) was added and the mixture was stirred at room or at the reflux temperature till completion of the hydrolysis, following the reaction by TLC. When no more starting ester remained, the organic solvent was removed in vacuo.

Work-up A: the aqueous residue was extracted with diethyl ether (3×10 ml). The combined organic phases were dried with anh. Na_2SO_4 and concentrated in vacuo, to give (*R*)- or (*S*)-**1**. The aqueous phase was acidified (pH=1) and was extracted with a mixture of *n*-pentane/CH_2Cl_2 in the ratio of 98:2 (3×20 ml). The combined organic phases were dried with anh. Na_2SO_4 and concentrated in vacuo, to give acids (1*R*,2*R*,4*R*)- or (1*S*,2*S*,4*S*)-**7**, (*R*)-**14** or (1*R*,2*R*,3*S*,4*S*)-**33**.

Work-up B: water (4 ml) was added and the mixture was extracted with CH_2Cl_2 (3×10 ml). The combined organic phases were dried with anh. Na_2SO_4 and concentrated in vacuo, to give (*R*)- or (*S*)-**1**. The aqueous phase was acidified (pH=1) and was extracted with CH_2Cl_2 (5×10 ml). The combined organic phases were dried with anh. Na_2SO_4 and concentrated in vacuo, to give acids (*R*)-**15** or (*S*)-**22**.

*3.4.1. (1*R,*2*R,*4*R*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1*R,*2*R,*4*R*)-7*

Following the above general procedure at room temperature, from (1*R*,2*R*,3′*R*,4*R*)-**6** (148 mg, 0.45 mmol) and $LiOH \cdot H_2O$ (81 mg, 1.93 mmol) and after work-up A, (1*R*,2*R*,4*R*)-**7** (60 mg, 96% yield) was obtained as an oil, $[\alpha]_D^{20}$=−142 (*c* 3.00, 95% ethanol), described: $[\alpha]_D^{20}$=−147 (*c* 3.00, 95% ethanol),[11] o.p. 97%.

*3.4.2. (1*S,*2*S,*4*S*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1*S,*2*S,*4*S*)-7*

Following the above general procedure at room temperature, from (1*S*,2*S*,3′*S*,4*S*)-**6** (140 mg, 0.43 mmol) and $LiOH \cdot H_2O$ (80 mg, 1.91 mmol) and after work-up A, (1*S*,2*S*,4*S*)-**7** (60 mg, quantitative yield) was obtained as an oil, $[\alpha]_D^{20}$=+140 (*c* 3.00, 95% ethanol), described for (1*R*,2*R*,4*R*)-**7**: $[\alpha]_D^{20}$=−147 (*c* 3.00, 95% ethanol),[11] o.p. 95%.

*3.4.3. (*R*)-4-Methylcyclohex-3-enecarboxylic acid (*R*)-14*

Following the above general procedure at room temperature, from (1*R*,3′*S*)-**11** (242 mg, 0.74 mmol) and $LiOH \cdot H_2O$ (47 mg, 1.11 mmol) and after work-up A, (*R*)-**14** (99 mg, 95% yield) was obtained as a solid, m.p. 98–99°C (ethyl acetate–hexane), $[\alpha]_D^{20}$=+94.5 (*c* 4.8, abs. ethanol), described for (*S*)-**11**: $[\alpha]_D^{20}$=−107 (*c* 4.00, abs. ethanol),[11] o.p. 88%.

*3.4.4. (*R*)-9,10-Dihydro-9,10-ethanoanthracene-11-carboxylic acid (*R*)-15*

Following the above general procedure at room temperature, from (11*R*,3′*S*)-**13** (219 mg, 0.50 mmol) and $LiOH \cdot H_2O$ (95 mg, 2.26 mmol) and after work-up B, (*R*)-**15** (124 mg, 99% yield) was obtained as a solid, m.p. 197.5–199.5°C (ethyl acetate), $[\alpha]_D^{20}$=−7.4 (*c* 1.8, $CHCl_3$), IR (KBr) ν: 3500–2600, max. at 3285 (O–H st), 1726 and 1688 (C=O st) cm^{-1}. $C_{17}H_{14}O_2$ (250.31): calcd: C, 81.57%; H, 5.64%. Found: C, 81.68%; H, 5.75%. ^{1}H NMR δ: 1.93 (ddd, *J*=12.5 Hz, *J*′=10.5 Hz, *J*′′=3.0 Hz, 1H, 12-H*anti*),

2.03 (ddd, J=12.5 Hz, J'=4.5 Hz, J''=2.5 Hz, 1H, 12-H*syn*), 2.82 (ddd, J=10.5 Hz, J'=4.5 Hz, J''=2.5 Hz, 1H, 11-H), 4.26 (t, J=2.5 Hz, 1H, 9-H), 4.60 (d, J=2.5 Hz, 1H, 10-H), 7.00-7.07 (complex signal, 4H, 2-H, 3-H, 6-H and 7-H), 7.17–7.24 (complex signal, 4H, 1-H, 4-H, 5-H and 8-H). ^{13}C NMR δ: 30.5 (CH_2, C12), 43.7 (CH, C9), 44.0 (CH, C11), 46.5 (CH, C10), 123.1 (CH), 123.5 (CH), 123.6 (CH), 125.0 (CH), 125.8 (2 CH), 126.2 (CH) and 126.3 (CH) (Ar-CH), 139.6 (C), 142.3 (C), 143.6 (C) and 143.7 (C) (Ar-C), 179.6 (C, COO).

3.4.5. (S)-9,10-Dihydro-11-methyl-9,10-ethanoanthracene-11-carboxylic acid (S)-**22**

Following the above general procedure at the reflux temperature, from (11*S*,3′*R*)-**21** (127 mg, 0.28 mmol) and $LiOH \cdot H_2O$ (53 mg, 1.26 mmol) and after work-up B, (*S*)-**22** (72 mg, 96% yield) was obtained as a solid, m.p. 140–142°C (diethylether–hexane), $[\alpha]_D^{20}$=−26.7 (*c* 1.08, $CHCl_3$), IR (KBr) ν: 3300–2400 (O–H st), 1699 (C=O st) cm^{-1}. $C_{18}H_{16}O_2$ (264.34): calcd: C, 81.79%; H, 6.11%. Found: C, 81.84%; H, 6.28%. ^{1}H NMR δ: 1.06 (s, 3H, 11-CH_3), 1.39 (dd, J=12.5 Hz, J'=2.5 Hz, 1H, 12-H*anti*), 2.61 (dd, J=12.5 Hz, J'=3.0 Hz, 1H, 12-H*syn*), 4.25 (t, J=2.5 Hz, 1H, 9-H), 4.36 (s, 1H, 10-H), 7.02–7.14 (complex signal, 4H, 2-H, 3-H, 6-H and 7-H), 7.20–7.30 (complex signal, 4H, 1-H, 4-H, 5-H and 8-H), 9–10 (broad s, 1H, COOH). ^{13}C NMR δ: 26.8 (CH_3, 11-CH_3), 38.6 (CH_2, C12), 44.4 (CH, C9), 48.4 (C, C11), 52.5 (CH, C10), 123.1 (CH), 123.3 (CH), 125.0 (CH), 125.5 (CH), 125.6 (CH), 126.0 (CH), 126.1 (CH) and 126.3 (CH) (Ar-CH), 140.4 (C), 141.1 (C), 143.1 (C) and 143.5 (C) (Ar-C), 182.0 (C, COO).

3.4.6. (1R,2R,3S,4S)-3-Methylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1R,2R,3S,4S)-**33**

Following the above general procedure at room temperature, from (1*R*,2*R*,3*S*,3′*R*,4*S*)-**27** (250 mg, 0.74 mmol) and $LiOH \cdot H_2O$ (130 mg, 3.10 mmol) and after work-up A, (1*R*,2*R*,3*S*,4*S*)-**33** (100 mg, 89% yield) was obtained as an oil, $[\alpha]_D^{20}$=−152 (*c* 1.00, ethanol 95%), described: $[\alpha]_D^{20}$=−157 (*c* 1.00, 95% ethanol),[39] o.p. 97%.

3.5. X-Ray crystal-structure determinations of (11R,3′S)-**13**

A prismatic crystal was selected and mounted on a Enraf–Nonius CAD4 four-circle diffractometer. Unit cell parameters were determined by automatic centering of 25 reflections ($12<\theta<21°$) and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo-$K\alpha$ radiation, using $\omega/2\theta$ scan technique. Two thousand, six hundred and three reflections were measured in the range $2.13\leq\theta\leq29.93$, of which 2577 were non-equivalent by symmetry [R_{int} (on I)=0.010]; 2064 reflections were assumed as observed by applying the condition $I>2\sigma(I)$. Three reflections were measured every 2 h as orientation and intensity control; significant intensity decay was not observed. Lorentz polarization but no absorption corrections were made. The structure was solved by direct methods, using the SHELXS computer program[41] and refined by the full-matrix least-squares method with the SHELX-93 computer program[42] using 2527 reflections (very negative intensities were not assumed). The function minimized was $\sum w(|F_o|^2-|F_c|^2)^2$, where $w=[\sigma^2(I)+(0.0762P)^2+0.0362P]^{-1}$, and $P=(|F_o|^2+2|F_c|^2)/3$. f, f′ and f″ were taken from the *International Tables of X-Ray Crystallography*.[43] The extinction coefficient was 0.013(2). The chirality of the structure was defined by the Flack coefficient, which is equal to 1.66(238) for the given results.[44] All H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor. Goodness of fit=1.122 for all observed reflections. Mean shift/e.s.d.=0.00. The results are shown in Table 1.[45]

Table 1
Experimental data of the X-ray crystal-structure determination of (11*R*,3′*S*)-**13**

Molecular formula	$C_{29}H_{27}NO_3$	F(000)	928
Molecular mass	437.52	*d*(calcd) [Mg m^{-3}]	1.242
Temperature (K)	293(2)	Size of crystal [mm]	0.1×0.1×0.2
Crystal system	Orthorhombic	Measured reflections	2603
Space group	$P2_12_12_1$	Independent reflections	2577
Cell parameters	[a]	Observed reflections	2064
a [Å]	6.943(4)	μ(Mo-*Kα*) [mm^{-1}][b]	0.080
b [Å]	17.609(12)	*R*	0.0540
c [Å]	19.13(2)	*Rw*	0.1181
α [°]	90	Absolute structure parameter	-2(2)
β [°]	90	Diff. Four. $\Delta\rho_{max}$[c] (eÅ^{-3})	0.185
γ [°]	90	$\Delta\rho_{min}$[d] (eÅ^{-3})	-0.177
V [Å^3]	2339(3)	Refined parameters	407
Z	4	Max. shift / e.s.d.	0.00

[a] Determined by automatic centering of 25 reflections ($12 < \theta < 21°$).
[b] Linear absorption coefficient. Radiation Mo-*Kα* (λ = 0.71069 Å).
[c] Maximum and [d] minimum peaks in final difference synthesis.

*3.6. X-Ray crystal-structure determinations of (11*S*,3′*R*)-**21***

A prismatic crystal was selected and mounted on a Enraf–Nonius CAD4 four-circle diffractometer. Unit cell parameters were determined by automatic centering of 25 reflections ($12<\theta<21°$) and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo-*Kα* radiation, using $\omega/2\theta$ scan technique. Two thousand, six hundred and sixty-nine reflections were measured in the range $2.34\leq\theta\leq29.97$, of which 2516 were non-equivalent by symmetry [R_{int} (on *I*)=0.020]; 2024 reflections were assumed as observed by applying the condition $I>2\sigma(I)$. Three reflections were measured every 2 h as orientation and intensity control; significant intensity decay was not observed. Lorentz polarization but no absorption corrections were made. The structure was solved by direct methods, using the SHELXS computer program[41] and refined by the full-matrix least-squares method with the SHELX-93 computer program[42] using 2466 reflections (very negative intensities were not assumed). The function minimized was $\sum w(|F_o|^2-|F_c|^2)^2$, where $w=[\sigma^2(I)+(0.0460P)^2+0.1157P]^{-1}$, and $P=(|F_o|^2+2|F_c|^2)/3$. f, f′ and f″ were taken from the *International Tables of X-Ray Crystallography*.[43] The extinction coefficient was 0.017(2). The chirality of the structure was defined by the Flack coefficient, which is equal to 0.96(197) for the given results.[44] Twenty-six H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor and 3 H atoms were computed and refined with an overall isotropic temperature factor by using a ‘riding’ model. Goodness of fit=1.127 for all observed reflections. Mean shift/e.s.d.=0.00. The results are shown in Table 2.[45]

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Table 2
Experimental data of the X-ray crystal-structure determination of (11*S*,3′*R*)-**21**

Molecular formula	$C_{30}H_{29}NO_3$	F(000)	480
Molecular mass	451.54	*d*(calcd) [Mg m^{-3}]	1.259
Temperature (K)	293(2)	Size of crystal [mm]	0.1×0.1×0.2
Crystal system	Monoclinic	Measured reflections	2669
Space group	$P2_1$	Independent reflections	2516
Cell parameters	[a]	Observed reflections	2024
a [Å]	8.816(4)	μ(Mo-*Kα*) [mm^{-1}][b]	0.081
b [Å]	15.533(9)	*R*	0.0526
c [Å]	8.868(3)	*Rw*	0.0997
α [°]	90°	Absolute structure parameter	1(2)
β [°]	101.19(4)	Diff. Four. $\Delta\rho_{max}$[c] (eÅ^{-3})	0.170
γ [°]	90	$\Delta\rho_{min}$[d] (eÅ^{-3})	-0.155
V [Å^3]	1191.3(10)	Refined parameters	413
Z	2	Max. shift / e.s.d.	0.00

[a] Determined by automatic centering of 25 reflections ($12 \le \theta \le 21°$).
[b] Linear absorption coefficient. Radiation Mo-*Kα* (λ = 0.71069 Å).
[c] Maximum and [d] minimum peaks in final difference synthesis.

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