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Diels–Alder reactions of phenylglycinol-derived bicyclic lactams. Enantiodivergent synthesis of *cis*-hydroisoquinolines

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Abstract—The diastereomeric phenylglycinol-derived unsaturated δ-lactams *trans*-**3** and *cis*-**3** react with dienes with *exo* facial diastereoselectivity to give the corresponding tricyclic adducts, which were ultimately converted to enantiomeric *cis*-hydroisoquinolines.

1. Introduction

Many bioactive natural and synthetic products incorporate a totally (or partially) reduced isoquinoline ring system. Among them, of particular interest are the indole alkaloids of the yohimbine-reserpine type,[1] which display a variety of therapeutic effects, and manzamines, a family of marine sponge metabolites that exhibit antitumor and antibiotic activity.[2]

Although the Diels–Alder reaction between 5,6-dihydro-2-pyridones and appropriate dienophiles has been extensively used to construct the functionalized *cis*-hydroisoquinoline skeleton in the racemic series, mainly in the context of the synthesis of manzamines,[3] the enantioselective version of the process has been little explored.[4]

In the context of our studies on the enantioselective synthesis of piperidine-containing derivatives from phenylglycinol-derived δ-lactams,[5,6] we report here an enantiodivergent synthetic entry to *cis*-hydroisoquinolines, the key step being an intermolecular Diels–Alder reaction on a bicyclic 5,6-dihydro-2-pyridone.

Related asymmetric Diels–Alder cycloadditions on L-valinol-derived unsaturated γ-lactams have been employed to provide isoindole-1-one cycloadducts with an excellent facial diastereoselectivity.[7]

2. Results and discussion

Previous work from lactams *trans*-**3** and *cis*-**3**, and related unsaturated δ-lactams, has revealed that under kinetic control they undergo conjugate addition reactions with high *exo* facial diastereoselectivity, the configuration of the new stereocenter generated in the process being determined by the configuration of the methine 8a carbon.[5a,b,e]

To study the stereochemical outcome of Diels–Alder cycloadditions we initially selected lactams *trans*-**3** and *cis*-**3**, which were prepared from the corresponding saturated lactams *trans*-**1** and *cis*-**1** via the respective selenides *trans*-**2** and *cis*-**2** as previously reported.[5a]

Diels–Alder reactions on *trans*-**3** using 2,3-dimethyl-1,3-butadiene **4a** and 2-methyl-1,3-butadiene **4b** as dienes were carried out either under high-pressure conditions (Method A) or using Lewis acid catalysis (Method B). In both cases the process was highly stereoselective as only the *exo* diastereomers, **5a** and **5b**, respectively, were isolated (Scheme 1). The absolute configuration of adduct **5a** was unambiguously proven by X-ray crystallography.[8] A similar facial diastereoselectivity was observed from the more activated diene **4c** under high pressure conditions. The resulting cycloadduct **5c** was isolated in 64% yield as a 3:1 epimeric mixture at C-6 and converted either to ketone **6** (one stereoisomer of absolute configuration at C-6 not determined) by treatment with TBAF or to enone **7** by treatment with 10% HF in acetonitrile (Scheme 2).

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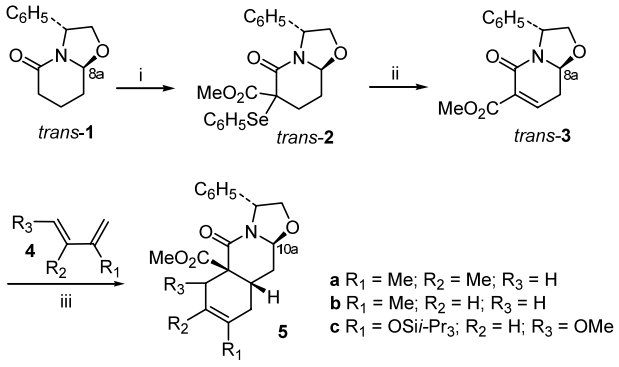
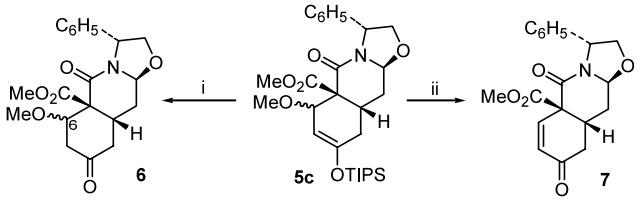
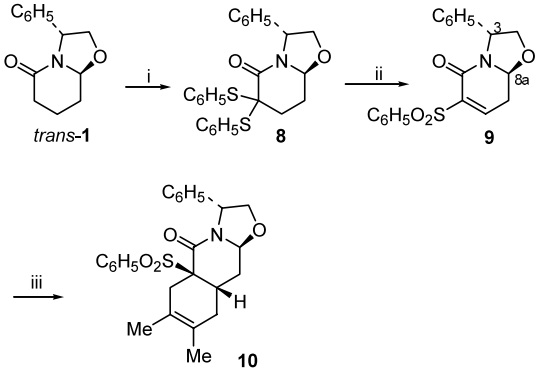


Scheme 1. *Reagents and conditions*: (i) LHMDS, $ClCO_2Me$, PhSeBr, THF, −78°C; (ii) O_3, CH_2Cl_2, −78°C, then O_2, 25°C; (iii) **4**, CH_2Cl_2, 12 kbar, or $ZnBr_2$, CH_2Cl_2.



Scheme 2. *Reagents and conditions*: (i) TBAF, THF, 3 h; (ii) 10% HF, MeCN, 2 h.

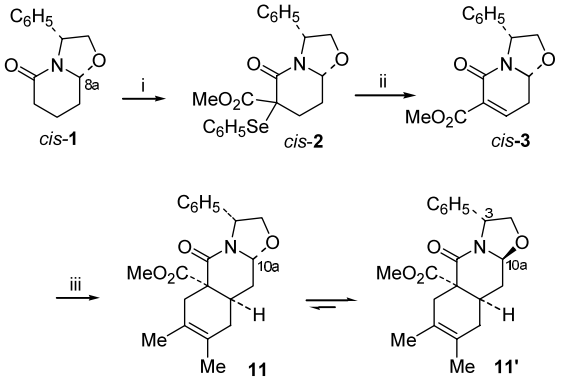
The same *exo* diastereoselectivity was observed in the Diels–Alder reaction between the 3,8a-*trans* unsaturated lactam **9** and butadiene **4a** (Scheme 3). This lactam, bearing a phenylsulfonyl instead of a methoxycarbonyl activating group, was prepared from *trans*-**1** via dithioacetal **8** and used without further purification because of its tendency to give the corresponding 2-pyridone.



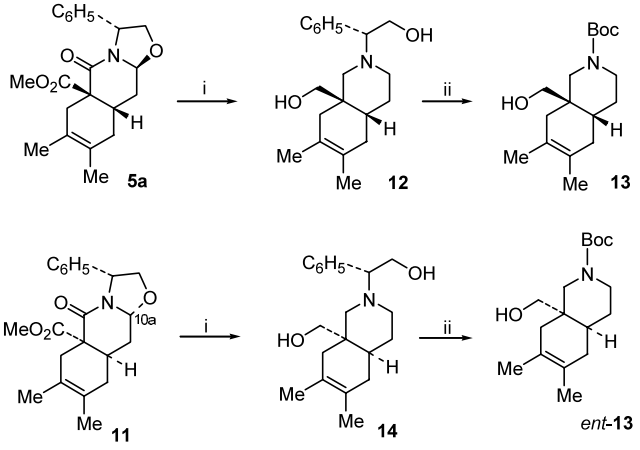
Scheme 3. *Reagents and conditions*: (i) LHMDS, *S*-phenyl benzene thiosulfonate, THF, −78°C; (ii) aq. $NaHCO_3$, then *m*-CPBA, CH_2Cl_2; (iii) 2,3-dimethyl-1,3-butadiene **4a**, CH_2Cl_2, 12 kbar, 22 h, rt.

We then studied the behavior of unsaturated lactam *cis*-**3** as dienophile in the Diels–Alder reaction with butadiene **4a**. Under high pressure conditions the *exo* adduct **11** was formed as the major product, whose absolute configuration was unambiguously confirmed by X-ray diffraction techniques[8] (Scheme 4). In this case minor amounts of the *endo* isomer were also isolated. In the presence of a Lewis acid catalyst the reaction led to hydroisoquinolone **11′** (the C-10a epimer of **11)** as the major product, a result that can be rationalized by considering that the initially formed cycloadduct **11** undergoes equilibration to the more stable 3,10a-*trans* isomer. A similar equilibration under acidic conditions from lactam *cis*-**1** to *trans*-**1** has been reported.[5a]

To compare the stereochemical outcome of the Diels–Alder reactions on lactams *trans*-**3** and *cis*-**3**, tricyclic adducts **5a** and **11** were treated with alane ($AlCl_3$/$LiAlH_4$), which caused the cleavage of the C–O bond of the oxazolidine ring and the simultaneous reduction of the ester and lactam carbonyl groups to give alcohols **12** and **14**, respectively (Scheme 5). In agreement with the proposed stereochemistry for the minor stereoisomers isolated in the Diels–Alder reactions from *cis*-**3**, a similar alane reduction from the *endo* isomer of **11** led



Scheme 4. *Reagents and conditions*: (i) LHMDS, $ClCO_2Me$, PhSeBr, THF, −78°C; (ii) O_3, CH_2Cl_2, −78°C, then O_2, 25°C; (iii) 2,3-dimethyl-1,3-butadiene **4a**, CH_2Cl_2, 12 kbar, 18 h, rt or $ZnBr_2$, CH_2Cl_2, 5 h, rt.

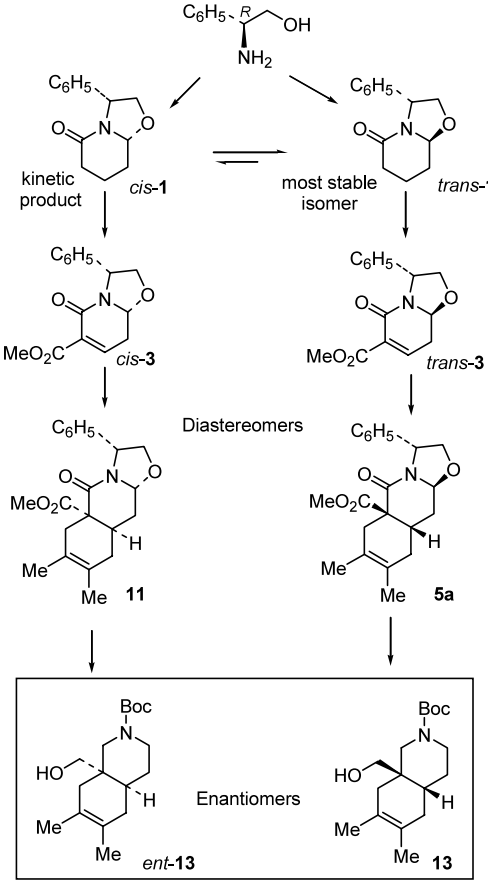


Scheme 5. *Reagents and conditions*: (i) $AlCl_3$, $LiAlH_4$, THF, −78 to 25°C; (ii) di-*tert*-butyl dicarbonate, EtOAc, $Pd(OH)_2$/C, H_2, 24 h, rt.

to **12** (50%), whereas the 10a epimer **11′** gave **14** (56%). Finally, removal of the chiral substituent on the piperidine nitrogen from the above diastereomeric *cis*-hydroisoquinolines **12** and **14** by hydrogenolysis in the presence of di-*tert*-butyl dicarbonate provided **13** and *ent*-**13**, respectively.

In conclusion, as in the kinetically controlled conjugate additions to related unsaturated δ-lactams reported previously,[5a,b,e] the approach of the diene in the cycloadditions here studied occurs stereoselectively from the convex face of the bicyclic lactam, *syn* with respect to the 8a methine proton.

In summary, we have developed an enantiodivergent synthetic entry to *cis*-hydroisoquinolines. Starting from a single isomer of phenylglycinol it is possible to gain access to the two enantiomeric series of *cis*-hydroisoquinolines by simply using either the kinetic bicyclic lactam *cis*-**1**, formed in the cyclodehydration of (*R*)-phenylglycinol with methyl 5-oxopentanoate, or the most stable isomer *trans*-**1**. Diels–Alder reactions on the respective α,β-unsaturated lactams *cis*-**3** and *trans*-**3** provide enantiopure diastereomeric *cis*-hydroisoquinolines, which are ultimately converted to the corresponding separate enantiomers (Scheme 6).



Scheme 6.

3. Experimental

3.1. General

Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located with aqueous potassium permanganate solution or with iodoplatinate reagent. Flash chromatography was carried out using SiO_2 (silica gel 60, SDS, 35–70 μ). All nonaqueous reactions were performed under an inert atmosphere. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried using standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HMRS were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

3.2. (3*R*,5a*R*,9a*S*,10a*S*)-5a-(Methoxycarbonyl)-7,8-dimethyl-5-oxo-3-phenyl-2,3,9,9a,10,10a-hexahydro-6*H*-oxazolo[3,2-*b*]isoquinoline 5a

A stream of ozone gas was bubbled through a cooled (−78°C) solution of the selenide *trans*-**2**[5a] (345 mg, 0.80 mmol) in anhydrous CH_2Cl_2 (20 mL) until it turned pale blue (ca. 30 min). The solution was purged with O_2 for 20 min, and the temperature was slowly raised to 25°C. After 30 min of stirring, the mixture was poured into brine (10 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated under reduced pressure (external temperature 25°C) to give the unsaturated lactam *trans*-**3** as an oil (348 mg), which was used in the next reaction without further purification.

Method A. A mixture of crude unsaturated lactam *trans*-**3** (120 mg), obtained from selenide *trans*-**2** (118 mg, 0.27 mmol) operating as above, and 2,3-dimethyl-1,3-butadiene **4a** (150 μL, 1.37 mmol) in anhydrous CH_2Cl_2 (4 mL) was allowed to react under a pressure of 12 kbar for 12 h at rt. The mixture was diluted with CH_2Cl_2, washed with brine, dried, and concentrated to give, after flash column chromatography (75:25 hexane–EtOAc), pure compound **5a** (59 mg, 61% from *trans*-**2**). IR (film) 1743, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3H), 1.65 (s, 3H), 1.83 (d, J=17.7 Hz, 1H), 2.06 (ddd, J=14.7, 5.0, 3.5 Hz, 1H), 2.16 (ddd, J=14.7, 10.0, 6.0 Hz, 1H), 2.24 (masked, 1H), 2.31 (d, J=18.0 Hz, 1H), 2.70–2.84 (m, 2H), 3.74 (s, 3H), 3.76 (dd, J=8.7, 7.5 Hz, 1H), 4.49 (app t, J=8.4 Hz, 1H), 4.99 (dd, J=5.7, 3.6 Hz, 1H), 5.38 (app t, J=7.8 Hz, 1H), 7.18–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_3), 18.9 (CH_3), 28.8 (CH_2), 30.0 (CH), 33.6 (CH_2), 33.8 (CH_2), 52.5 (CH_3), 54.5 (C), 58.1 (CH), 71.5 (CH_2), 85.8 (CH), 122.9 (C), 123.0 (C), 125.7 (2 CH), 127.4 (CH), 128.7 (2 CH), 139.6 (C), 169.9 (C), 172.0 (C); MS [EI, m/z (%)] 355 (M^+, 15), 296 (90), 91 (100), 77 (54);

$[\alpha]_D^{22}$ −13.0 (*c* 1.15, $CHCl_3$). Anal. calcd for $C_{21}H_{25}NO_4 \cdot 1/4\ H_2O$: C, 70.08; H, 7.14; N, 3.89. Found: C, 70.30; H, 7.02; N, 3.88.

Method B. A solution of the above crude unsaturated lactam *trans*-**3** in anhydrous CH_2Cl_2 (15 mL) was added to a suspension of anhydrous $ZnBr_2$ (197 mg, 0.87 mmol) in CH_2Cl_2 (5 mL). Then, an excess of 2,3-dimethyl-1,3-butadiene **4a** (0.5 mL, 4.42 mmol) was added dropwise, and the mixture was stirred under argon at rt for 4 h 30 min. The mixture was washed with brine, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting oil was chromatographed (3:1 hexane–EtOAc) to give pure compound **5a** (184 mg, 65% from *trans*-**2**).

3.3. (3*R*,5a*R*,9a*S*,10a*S*)-5a-(Methoxycarbonyl)-8-methyl-5-oxo-3-phenyl-2,3,9,9a,10,10a-hexahydro-6*H*-oxazolo-[3,2-*b*]isoquinoline 5b

Method A. A mixture of crude unsaturated lactam *trans*-**3**, obtained from selenide *trans*-**2** (250 mg, 0.58 mmol) operating as above, and 2-methyl-1,3-butadiene **4b** (0.29 mL, 2.90 mmol) in anhydrous CH_2Cl_2 (3 mL) was allowed to react under a pressure of 12 kbar for 24 h at rt. The mixture was diluted with CH_2Cl_2, washed with brine, dried, and concentrated to give, after flash column chromatography (8:2 hexane–EtOAc), compound **5b** (79 mg, 40% from *trans*-**2**). IR (film) 1747, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 3H), 1.82 (d, $J=17.7$ Hz, 1H), 2.09 (ddd, $J=14.7$, 5.7, 2.7 Hz, 1H), 2.19 (ddd, $J=14.7$, 10.8, 6.2 Hz, 1H), 2.22 (masked, 1H), 2.35 (dm, $J=17.8$, Hz, 1H), 2.83–2.96 (m, 2H), 3.75 (s, 3H), 3.77 (dd, $J=9.0$, 7.4 Hz, 1H), 4.49 (app t, $J=8.2$ Hz, 1H), 5.00 (dd, $J=6.3$, 2.7 Hz, 1H), 5.37–5.43 (m, 2H), 7.18–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_3), 27.5 (CH_2), 28.3 (CH_2), 29.4 (CH), 32.0 (CH_2), 52.5 (CH_3), 53.5 (C), 58.1 (CH), 71.4 (CH_2), 85.7 (CH), 117.6 (CH), 125.7 (2 CH), 127.4 (CH), 128.7 (2 CH), 131.1 (C), 139.6 (C), 170.3 (C), 171.7 (C); MS [EI, *m*/*z* (%)] 341 (M^+, 9), 310 (10), 282 (88), 91 (100), 77 (62); $[\alpha]_D^{22}$ −15.3 (*c* 1.08, $CHCl_3$). Anal. calcd for $C_{20}H_{23}NO_4 \cdot 3/2\ H_2O$: C, 66.01; H, 7.06; N, 3.85. Found: C, 65.67; H, 6.67; N, 3.61.

Method B. Anhydrous $ZnBr_2$ (259 mg, 1.15 mmol) and 2-methyl-1,3-butadiene **4b** (575 μL, 5.75 mmol) were added to a solution of crude unsaturated lactam *trans*-**3**, obtained from selenide *trans*-**2** (495 mg, 1.15 mmol) operating as above, in anhydrous CH_2Cl_2 (5 mL). The resulting mixture was stirred under argon at rt for 16 h and then poured into brine. The aqueous layer was washed with EtOAc (10 mL) and CH_2Cl_2. The combined organic extracts were dried and concentrated to give an oil, which was chromatographed (3:1 hexane–EtOAc) to give pure **5b** (165 mg, 42% from *trans*-**2**).

3.4. (3*R*,5a*R*,9a*S*,10a*S*)-6-Methoxy-6a-(methoxycarbonyl)-5-oxo-3-phenyl-8-(triisopropylsilyloxy)-2,3,9,9a,10,10a-hexahydro-6*H*-oxazolo[3,2-*b*]isoquinoline 5c

A mixture of unsaturated lactam *trans*-**3**, obtained as above from selenide *trans*-**2** (239 mg, 0.55 mmol), and 1-methoxy-3-(triisopropylsilyloxy)-1,3-butadiene **4c** (500 mg, 1.94 mmol) in anhydrous CH_2Cl_2 (5 mL) was allowed to react under a pressure of 12 kbar for 24 h at rt. The mixture was diluted with CH_2Cl_2, washed with brine, dried, and concentrated. Flash chromatography (4:1 hexane–EtOAc) of the residue gave the two C-6 epimers of **5c** (146 mg, 49%; 45 mg, 15%). Major epimer: IR (film) 1745, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (cs, 18 H), 1.15 (m, 3H), 1.97 (d, $J=17.7$ Hz, 1H); 2.08 (dd, $J=14.5$, 6.5 Hz, 1H), 2.35 (ddm, $J=17.7$, 6.6 Hz, 1H), 2.61 (ddd, $J=14.5$, 14.5, 7.0 Hz, 1H), 3.00 (m, 1H), 3.29 (s, 3H), 3.72 (m, 3H), 3.74 (dd, $J=8.7$, 7.2 Hz, 1H), 4.50 (app t, $J=8.4$ Hz, 1H), 4.61 (d, $J=5.1$ Hz, 1H), 4.94 (d, $J=6.3$ Hz, 1H), 5.19 (dd, $J=5.5$, 1.0 Hz, 1H), 5.32 (app t, $J=7.5$ Hz, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.5 (3 CH), 17.8 (6 CH_3), 28.6 (CH), 28.7 (CH_2), 32.4 (CH_2), 52.5 (CH_3), 57.2 (CH), 57.4 (C), 58.3 (CH_3), 71.7 (CH_2), 75.5 (CH), 86.0 (CH), 100.1 (CH), 125.7 (2 CH), 127.2 (CH), 128.5 (2 CH), 139.8 (C), 151.8 (C), 166.9 (C), 169.8 (C). Minor epimer: IR (film) 1737, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (cs, 18H), 1.18 (m, 3H), 2.16 (dd, $J=18.0$, 9.0 Hz, 1H), 2.31 (m, 2H), 2.52 (ddd, $J=10.0$, 8.5, 1.5 Hz, 1H), 3.20 (m, 1H), 3.26 (s, 3H), 3.74 (dd, $J=9.0$, 7.5 Hz, 1H), 3.77 (s, 3H), 4.52 (app t, $J=8.4$ Hz, 1H), 4.67 (d, $J=6.0$ Hz, 1H), 5.05 (dd, $J=8.4$, 6.0 Hz, 1H), 5.12 (d, $J=6.0$ Hz, 1H), 5.25 (app t, $J=7.8$ Hz, 1H), 7.10–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.6 (3 CH), 17.9 (6 CH_3), 28.3 (CH), 29.8 (CH_2), 31.5 (CH_2), 52.9 (CH_3), 56.2 (CH_3), 57.4 (C), 58.5 (CH), 72.8 (CH_2), 77.2 (CH), 86.0 (CH), 99.2 (CH), 125.6 (2 CH), 127.4 (CH), 128.7 (2 CH), 139.4 (C), 154.3 (C), 163.6 (C), 169.4 (C).

3.5. (3*R*,5a*S*,9a*R*,10a*S*)-6-Methoxy-5a-(methoxycarbonyl)-5,8-dioxo-3-phenyl-2,3,6,7,9,9a,10,10a-octahydro-8*H*-oxazolo[3,2-*b*]isoquinoline 6

TBAF (100 mg, 0.32 mmol) was added to a solution of compound **5c** (146 mg, 0.27 mmol, major epimer) in THF (5 mL), and the mixture was stirred with an external ice-bath for 3 h. A saturated aqueous NH_4Cl solution was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the residue was chromatographed (3:2 hexane–EtOAc) to give ketone **6** (92 mg, 89%) as a solid. IR (KBr) 1743, 1715, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26–2.38 (m, 3H), 2.58–2.75 (m, 2H), 2.87 (dd, $J=18.0$, 3.8 Hz, 1H), 2.90 (dd, $J=16.0$, 14.0 Hz, 1H), 3.15 (s, 3H), 3.74 (dd, $J=9.0$, 8.0 Hz, 1H), 3.76 (s, 3H), 4.41 (dd, $J=3.8$, 2.4 Hz, 1H), 4.57 (dd, $J=9.0$, 7.8 Hz, 1H), 5.13 (dd, $J=7.8$, 5.4 Hz, 1H), 5.33 (app t, $J=8.0$ Hz, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.4 (CH_2), 31.5 (CH), 40.6 (CH_2), 42.0 (CH_2), 53.0 (CH_3), 56.7 (C), 58.1 (CH_3), 59.1 (CH), 72.8 (CH_2), 78.7 (CH), 85.3 (CH), 125.8 (2 CH), 127.5 (CH), 128.6 (2 CH), 138.7 (C), 164.5 (C), 171.2 (C), 208.1 (C); mp 101–103°C. Anal. calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.20; H, 6.37; N, 3.76.

3.6. (3*R*,5a*S*,9a*R*,10a*S*)-5a-(Methoxycarbonyl)-5,8-dioxo-3-phenyl-2,3,9,9a,10,10a-hexahydro-8*H*-oxazolo-[3,2-*b*]isoquinoline 7

A solution of 10% HF in MeCN (4.4 mL) was added to a solution of the crude Diels–Alder adduct **5c**, obtained

operating as above from selenide *trans*-**2** (610 mg, 1.42 mmol), in MeCN (7 mL). The resulting mixture was stirred for 2 h at rt. Saturated aqueous $NaHCO_3$ was added, and the mixture was diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with additional CH_2Cl_2. The combined organic extracts were dried and concentrated. Purification of the residue by flash chromatography (35:65 hexane–EtOAc) afforded pure enone **7** (234 mg, 48% from *trans*-**2**). IR (KBr) 1736, 1690, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25–2.39 (m, 2H), 2.55–2.65 (m, 2H), 3.04 (m, 1H), 3.82 (s, 3H), 3.83 (dd, $J=9.0$, 8.0 Hz, 1H), 4.60 (dd, $J=9.0$, 8.0 Hz, 1H), 5.15 (dd, $J=8.4$, 5.6 Hz, 1H), 5.33 (t, $J=8.0$ Hz, 1H), 6.19 (d, $J=10.4$ Hz, 1H), 7.12 (d, $J=10.4$ Hz, 1H), 7.20 (dm, $J=8.4$ Hz, 2H), 7.24–7.36 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.4 (CH_2), 34.1 (CH), 39.8 (CH_2), 53.6 (CH_3), 55.7 (C), 58.9 (CH), 72.8 (CH_2), 86.1 (CH), 126.0 (2 CH), 128.0 (CH), 128.9 (2 CH), 129.4 (CH), 138.7 (C), 146.0 (CH), 163.9 (C), 170.6 (C), 195.8 (C); $[\alpha]_D^{22}$+3.1 (*c* 0.32, EtOH). HRMS calcd for $C_{19}H_{19}NO_5$ 341.1263, found 341.1273.

3.7. (3*R*,8a*S*)-5-Oxo-3-phenyl-6,6-bis(phenylsulfanyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine 8

Lithium bis(trimethylsilyl)amide (9 mL, 1.0 M in THF) was slowly added at −78°C to a solution of lactam *trans*-**1** (651 mg, 3.0 mmol) in anhydrous THF (30 mL), and the resulting mixture was stirred for 1 h. Then, a solution of *S*-phenyl benzenethiosulfonate (2.25 g, 9.0 mmol) in anhydrous THF (7.5 mL) was slowly added, and the mixture was stirred for 90 min at −78°C, warmed to rt, and poured into brine. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography of the resulting oil (7:3 hexane–EtOAc) afforded pure compound **8** (1.1 g, 85%). IR (KBr) 1657 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88–1.95 (m, 2H), 1.98–2.10 (m, 2H), 3.74 (dd, $J=9.0$, 8.1 Hz, 1H), 4.46 (dd, $J=9.0$, 7.8 Hz, 1H), 4.74 (dd, $J=7.2$, 6.3 Hz, 1H), 5.28 (app t, $J=7.8$ Hz, 1H), 7.10–7.20 (m, 4H), 7.25–7.45 (m, 9H), 7.74 (dm, $J=7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1 (CH_2), 28.3 (CH_2), 59.1 (CH), 64.8 (C), 72.6 (CH_2), 88.4 (CH), 126.8 (2 CH), 127.7 (CH), 128.6 (2 CH), 128.8 (2 CH), 129.2 (CH), 129.8 (CH), 129.9 (C), 131.4 (C), 136.3 (2 CH), 137.2 (2 CH), 138.8 (C), 166.2 (C); mp 144–146°C; $[\alpha]_D^{22}$ −49.0 (*c* 0.5, $CHCl_3$). Anal. calcd for $C_{25}H_{23}NO_2S_2$: C, 69.25; H, 5.35; N, 3.23; S, 14.79. Found: C, 69.40; H, 5.38; N, 3.15; S, 14.78.

3.8. (3*R*,5a*R*,9a*S*,10a*S*)-5a-(Benzenesulfonyl)-7,8-dimethyl-5-oxo-3-phenyl-2,3,9,9a,10,10a-hexahydro-6*H*-oxazolo[3,2-*b*]isoquinoline 10

Aqueous $NaHCO_3$ (0.5 M, 5 mL) was added to a solution of compound **8** (216 mg, 0.5 mmol) in CH_2Cl_2 (5 mL). Then, *m*-CPBA (70% of purity, 370 mg, 1.5 mmol) was added in small portions. The resulting mixture was stirred at rt for 3 h and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with aqueous $NaHCO_3$, dried, and concentrated to give sulfone **9**. The crude mixture was dissolved in CH_2Cl_2 (8 mL), 2,3-dimethyl-1,3-butadiene **4a** (200 μL, 1.75 mmol) was added, and the mixture was allowed to react under a pressure of 12 kbar for 22 h at rt. The solvent was eliminated under reduced pressure, and the residue was chromatographed (65:35 hexane–EtOAc) to give adduct **10** (87 mg, 40% from **8**). IR (KBr) 1659, 1296, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.61 (s, 3H), 2.18 (dd, $J=17.0$, 8.0 Hz, 1H), 2.80 (m, 2H), 2.31 (ddd, $J=13.5$, 5.4, 3.0 Hz, 1H), 2.47 (dd, $J=17.0$, 8.5 Hz, 1H), 2.70 (ddd, $J=13.5$, 9.3, 4.2 Hz, 1H), 3.39 (m, 1H), 3.74 (dd, $J=9.0$, 7.8 Hz, 1H), 4.64 (dd, $J=9.0$, 8.4 Hz, 1H), 5.09 (dd, $J=9.3$, 5.4 Hz, 1H), 5.32 (app t, $J=8.0$ Hz, 1H), 7.1 (m, 2H), 7.18–7.33 (m, 3H), 7.45–7.55 (m, 2H),7.60 (m, 1H), 7.85–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3), 18.9 (CH_3), 29.9 (CH), 30.8 (CH_2), 35.4 (CH_2), 36.4 (CH_2), 59.2 (CH), 71.5 (C), 73.2 (CH_2), 86.5 (CH), 123.3 (C), 125.4 (2 CH), 125.7 (C), 127.5 (CH), 128.3 (2 CH), 128.8 (2 CH), 131.0 (2 CH), 133.7 (CH), 137.1 (C), 139.2 (C), 163.9 (C); mp 123–125°C; $[\alpha]_D^{22}$ −5.5 (*c* 0.3, EtOH). Anal. calcd for $C_{25}H_{27}NO_4S$: C, 68.63; H, 6.22; N, 3.20; S, 7.33. Found: C, 68.31; H, 6.39; N, 3.12; S, 6.98.

3.9. (3*R*,5a*S*,9a*R*,10a*R*)-5a-(Methoxycarbonyl)-7,8-dimethyl-5-oxo-3-phenyl-2,3,9,9a,10,10a-hexahydro-6*H*-oxazolo[3,2-*b*]isoquinoline 11

Method A. The unsaturated lactam *cis*-**3** was prepared from selenide *cis*-**2**[5a] (350 mg, 0.81 mmol) following the experimental procedure above described for the preparation of *trans*-**3**. To a solution of the crude mixture of *cis*-**3** in CH_2Cl_2 (4 mL) was added 2,3-dimethyl-1,3-butadiene **4a** (320 μl, 2.83 mmol), and the mixture was allowed to react under a pressure of 12 kbar for 18 h at rt. The solvent was eliminated under reduced pressure, and the residue was purified by flash column chromatography (3:2 hexane–EtOAc) affording isoquinoline **11** (118 mg, 40% from *cis*-**2**) and the *endo* isomer (20 mg, 7%). Crystallization from Et_2O–hexane afforded pure **11**: IR (KBr) 1745, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.64 (s, 3H), 1.95 (dd, $J=17.2$, 6.0 Hz, 1H), 2.13–2.21 (m, 2H), 2.25 (ddd, $J=13.2$, 7.6, 6.0 Hz, 1H), 2.44 (br s, 2H), 2.84 (app q, $J=6.0$ Hz, 1H), 3.55 (s, 3H), 4.05 (dd, $J=9.0$, 2.0 Hz, 1H), 4.18 (dd, $J=9.0$, 7.2 Hz, 1H), 4.84 (dd, $J=7.2$, 2.0 Hz, 1H), 5.01 (dd, $J=7.6$, 6.0 Hz, 1H), 7.20–7.25 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7 (CH_3), 18.9 (CH_3), 30.2 (CH_2), 32.2 (CH), 33.8 (CH_2), 52.4 (CH_3), 54.6 (C), 58.7 (CH), 74.2 (CH_2), 86.3 (CH), 123.3 (C), 123.8 (C), 126.7 (2 CH), 127.6 (CH), 128.3 (2 CH), 140.7 (C), 166.7 (C), 172.6 (C); mp 227–230°C; MS [EI, *m*/*z* (%)] 355 (M^+, 12), 296 (100), 133 (38), 91 (54). HRMS calcd for $C_{21}H_{25}NO_4$ 355.1783, found 355.1782; $[\alpha]_D^{22}$ −131.3 (*c* 0.6, MeOH). Anal. calcd for $C_{21}H_{25}NO_4$ 1/4 H_2O: C, 70.08; H, 7.14; N, 3.89. Found: C, 70,17; H, 6.92; N, 3.77. *endo* Isomer of **11**: IR (KBr) 1747, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 6H), 1.75–1.99

(m, 1H), 2.20 (dt, $J=12.6$, 3.6 Hz, 2H), 2.50 (d, $J=17.4$ Hz, 1H), 2.72 (ddd, $J=9.3$, 6.3, 3.0 Hz, 1H), 3.69 (s, 3H), 4.07 (dd, $J=9.3$, 1.2 Hz, 1H), 4.18 (dd, $J=9.3$, 6.9 Hz, 1H), 4.84 (dd, $J=6.9$, 1.2 Hz, 1H), 4.98 (dd, $J=9.9$, 4.2 Hz, 1H), 7.30–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.4 (CH_3), 18.8 (CH_3), 31.5 (CH), 31.6 (CH_2), 33.6 (CH_2), 34.9 (CH_2), 52.5 (CH_3), 54.2 (C), 58.5 (CH), 73.8 (CH_2), 87.9 (CH), 121.8 (C), 122.0 (C), 126.6 (2 CH), 127.6 (CH), 128.4 (2 CH), 140.7 (C), 166.9 (C), 171.9 (C); $[\alpha]_D^{22}$ +34.7 (*c* 0.76, MeOH).

Method B. Anhydrous $ZnBr_2$ (211 mg, 0.94 mmol) and 2-methyl-1,3-butadiene **4b** (500 μL, 4.45 mmol) were added to a solution of crude unsaturated lactam *cis*-**3**, obtained from selenide *cis*-**2** (350 mg, 0.81 mmol) operating as above, in anhydrous CH_2Cl_2 (4 mL). The resulting mixture was stirred under argon at rt for 5 h and then poured into brine. The aqueous layer was washed with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The resulting oil was chromatographed (3:2 hexane–EtOAc) to give **11′** (81 mg, 28% from *cis*-**2**) and **11** (9 mg, 3%). **11′**: IR (KBr) 1749, 1650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.65 (s, 3H), 1.78–1.84 (m, 2H), 2.18 (dd, $J=5.6$, 3.2 Hz, 1H), 2.22 (dd, $J=5.6$, 3.2 Hz, 1H), 2.30 (d, $J=18$ Hz, 1H), 2.70–2.75 (m, 2H), 3.73 (dd, $J=8.8$, 1.6 Hz, 1H), 3.72 (s, 3H), 4.51 (t, $J=8.8$ Hz, 1H), 5.08 (dd, $J=7.6$, 5.6 Hz, 1H), 5.23 (t, $J=8.0$ Hz, 1H), 7.22–7.35 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.4 (CH_3), 18.9 (CH_3), 30.9 (CH_2), 31.3 (CH), 34.3 (CH_2), 34.8 (CH_2), 52.8 (CH_3), 53.9 (C), 58.1 (CH), 72.6 (CH_2), 87.5 (CH), 122.1 (C), 122.6 (C), 125.6 (2 CH), 127.5 (CH), 128.8 (2 CH), 139.3 (C), 168.0 (C), 172.0 (C); mp 130–132°C; MS [EI, *m*/*z* (%)] 355 (M^+, 21), 296 (100), 297 (22), 133 (29); $[\alpha]_D^{22}$ −2.2 (*c* 0.98, MeOH). Anal. calcd for $C_{21}H_{25}NO_4 \cdot 1/4H_2O$: C, 70.08; H, 7.14; N, 3.89. Found: C, 69.97; H, 7.09; N, 3.98.

3.10. (4a*R*,8a*S*)-8a-(Hydroxymethyl)-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6,7-dimethyl-2,3,4,4a,5,8-hexahydro-1*H*-isoquinoline 12

$LiAlH_4$ (256 mg, 6.75 mmol) was added to a suspension of $AlCl_3$ (300 mg, 2.25 mmol) in anhydrous THF (20 mL) at 0°C, and the mixture was stirred under argon at 25°C for 30 min. The temperature was lowered to −78°C, adduct **5a** (268 mg, 0.75 mmol) in anhydrous THF (15 mL) was slowly added, and the resulting suspension was stirred at rt for 24 h. The mixture was cooled to 0°C, and the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue was chromatographed (35:65 hexane–EtOAc) to give pure compound **12** (160 mg, 67%). IR (KBr) 3405 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.57 (s, 3H), 1.61 (s, 3H), 1.55–1.70 (m, 3H), 1.78 (d, $J=11.2$ Hz, 1H), 2.18 (d, $J=17.6$ Hz, 1H), 2.30 (td, $J=10.8$, 3.0 Hz, 1H), 2.40 (d, $J=17.2$ Hz, 1H), 2.59 (dd, $J=11.2$, 1.2 Hz, 1H), 2.81 (d, $J=10.8$ Hz, 1H), 3.39 (d, $J=10.8$ Hz, 1H), 3.39 (d, $J=10.8$ Hz, 1H), 3.62–3.75 (m, 2H), 3.98 (dd, $J=10.0$, 9.6 Hz, 1H), 7.19 (m, 2H), 7.28–7.37 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8 (CH_3), 19.1 (CH_3), 29.1 (CH_2), 33.8 (CH), 35.0 (CH_2), 37.5 (C), 52.2 (CH_2), 52.9 (CH_2), 60.4 (CH_2), 68.5 (CH_2), 70.2 (CH), 121.9 (C), 122.2 (C), 127.8 (CH), 128.2 (2 CH), 128.9 (2 CH), 135.6 (C); $[\alpha]_D^{22}$ −4.6 (*c* 0.2, MeOH). HRMS calcd for $C_{20}H_{29}NO_2$ 315.2198, found 315.2186. Anal. calcd for $C_{20}H_{29}NO_2 \cdot 1/2H_2O$: C, 74.04; H, 9.32; N, 4.32. Found: C, 73.63; H, 9.19; N, 4.14.

3.11. (4a*S*,8a*R*)-8a-(Hydroxymethyl)-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6,7-dimethyl-2,3,4,4a,5,8-hexahydro-1*H*-isoquinoline 14

Operating as above described for **12**, starting from lactam **11** (300 mg, 0.84 mmol), pure compound **14** (170 mg, 64%) was obtained after flash chromatography (EtOAc). IR (KBr) 3404 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–1.43 (m, 3H), 1.57 (s, 3H), 1.61 (s, 3H), 1.49–1.70 (m, 2H), 1.77 (tm, $J=10.5$ Hz, 1H), 2.18 (dm, $J=17.6$ Hz, 1H), 2.27 (d, $J=11.2$ Hz, 1H), 2.48 (d, $J=17.2$ Hz, 1H), 2.56 (d, $J=11.2$ Hz, 1H), 2.83 (dm, $J=10.5$ Hz, 1H), 3.37 (d, $J=10.4$ Hz, 1H), 3.43 (d, $J=10.4$ Hz, 1H), 3.61–3.72 (m, 2H), 4.01 (m, 1H), 7.19 (dm, $J=8.0$ Hz, 2H), 7.28–7.37 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.9 (CH_3), 19.1 (CH_3), 28.9 (CH_2), 33.9 (CH), 33.9 (CH_2), 35.0 (CH_2), 38.1 (C), 46.2 (CH_2), 58.7 (CH_2), 60.5 (CH_2), 68.4 (CH_2), 69.9 (CH), 121.8 (C), 122.3 (C), 127.8 (CH), 128.2 (2 CH), 128.9 (2 CH), 135.6 (C); $[\alpha]_D^{22}$ −4.5 (*c* 0.25, MeOH). HRMS calcd for $C_{20}H_{29}NO_2$ 315.2198, found 315.2194.

3.12. (4a*R*,8a*S*)-2-(*tert*-Butoxycarbonyl)-8a-(hydroxymethyl)-6,7-dimethyl-3,4,4a,5,8,8a-hexahydro-1*H*-isoquinoline 13

A solution of **12** (160 mg, 0.5 mmol) and di-*tert*-butyl dicarbonate (218 mg, 1 mmol) in EtOAc (10 mL) containing 20% $Pd(OH)_2/C$ (32 mg) was hydrogenated at rt for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting oil was chromatographed (8:2 EtOAc–hexane) affording pure compound **13** (105 mg, 71%) as a transparent oil. IR (film) 3456, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37–1.41 (m, 2H), 1.46 (s, 9 H), 1.40–1.45 (m, 2H), 1.59 (s, 3H), 1.60 (s, 3H), 1.62–1.80 (m, 2H), 1.98 (br d, $J=17.7$ Hz, 1H), 2.25 (d, $J=18$ Hz, 1H), 2.87 (d, $J=13.2$ Hz, 2H), 3.36 (d, $J=11.1$ Hz, 1H), 3.53 (d, $J=11.1$ Hz, 1H), 3.63 (dd, $J=13.2$, 1.2 Hz, 1H), 3.95 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.8 (CH_3), 19.0 (CH_3), 28.0 (CH_2), 28.5 (CH_3), 33.3 (CH), 33.6 (CH), 35.1 (CH_2), 38.0 (C), 43.4 (CH_2), 49.3 (CH_2), 67.4 (CH_2), 79.4 (C), 122.1 (C), 122.3 (C), 155.5 (C); $[\alpha]_D^{22}$ +5.0 (*c* 2.0, MeOH). Anal. calcd for $C_{17}H_{27}NO_3 3/2 H_2O$: C, 63.72; H, 9.44; N, 4.37. Found: C: 63.76; H, 9.43; N, 4.29.

3.13. (4a*S*,8a*R*)-2-(*tert*-Butoxycarbonyl)-8a-(hydroxymethyl)-6,7-dimethyl-3,4,4a,5,8,8a-hexahydro-1*H*-isoquinoline (*ent*-13)

Operating as in the above preparation of **13**, starting from compound **14** (140 mg, 0.39 mmol), pure *ent*-**13** (70 mg, 65%) was obtained. $[\alpha]_D^{22}$ −5.5 (*c* 2.0, MeOH).

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8. The experiment was done on an Enraf–Nonius CAD4 diffractometer using graphite-monochromated Mo Kα radiation. The structure was solved by direct methods using SHELXS-97 [Sheldrick, G. M., 1997, SHELX-97. Programs for Crystal Structure Analysis (Release 97-2), University of Göttingen, Germany] after applying Lorentz, polarization, and absorption (semiempirical PSI scan method) corrections. Full-matrix least squares refinement (SHELXL-97) with anisotropic thermal parameters for non-H atoms and riding thermal parameters for H-atoms (positioned at calculated positions) converged to a *R* factor of 0.0815 (for **5a**) and 0.0956 (for **11**) (calculated for the reflections with $I>2\sigma(I)$). **5a**: Crystal data: $C_{21}H_{25}NO_4$, monoclinic, space group $P2_1$, $a=10.0358(15)$, $b=7.6157(15)$, $c=12.502(2)$ Å, $\beta=95.490(16)°$, $V=951.1(3)$ Å^3, $Z=2$, μ(Mo Kα)$=0.086$ mm^{-1}, $D_{calcd}=1.241$ g/cm^3. Approximate dimensions: 0.60×0.60×0.16 mm^3. Data collection was up to a resolution of $2\theta=60.8°$ producing 5732 unique reflections. Largest peak and hole at the final difference Fourier synthesis were 0.370 and –0.407 e Å^{-3}. CCDC deposition number 209021. **11**: Crystal data: $C_{21}H_{25}NO_4$, monoclinic, space group $P2_1$, $a=12.449(5)$, $b=6.844(11)$, $c=22.832(14)$ Å, $\beta=104.19(5)°$, $V=1886(3)$ Å^3, $Z=4$, μ(Mo Kα)$=0.086$ mm^{-1}, $D_{calcd}=1.252$ g/cm^3. Data collection was up to a resolution of $2\theta=60.1°$ producing 5937 unique reflections. Largest peak and hole at the final difference Fourier synthesis were 0.323 and –0.372 e Å^{-3}. Calculations were done using the WinGX package (Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837–838). CCDC deposition number 209022.