Effective enantioselective approach to α-aminoalkylacrylic acid derivatives *via* a synthetic equivalent of an asymmetric Baylis–Hillman reaction: application to the synthesis of two C-2′ hydroxymethyl analogues of docetaxel

COMMUNICATION
1 PERKIN

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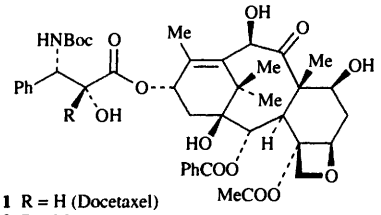
Two C-2′ hydroxymethyl analogues of docetaxel have been synthesized from 10-desacetyl baccatin III and enantiopure (3*S*)-3-(*N*-*tert*-butoxycarbonylamino)-2-methylene-3-phenylpropanoic acid; the latter was prepared *via* the use of a new method, which is discussed, as is the biological evaluation of the two new analogues.

The efficacy of paclitaxel (Taxol®) and its semisynthetic congener docetaxel (Taxotere®) (Scheme 1) in the treatment of



1 R = H (Docetaxel)
2 R = Me

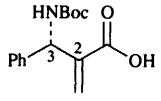
Scheme 1

certain cancers is now well established. However, the search for new drugs that display even broader activity and lower toxicity continues to foster considerable synthetic work. In this context, side-chain modified derivatives are of particular interest in that they offer relative ease of access.[1]

We recently reported the stereoselective preparation of the first alkylated docetaxel analogue **2** (Scheme 1), obtained by esterification of the protected C-2 methylated 2*R*,3*S* side chain of docetaxel with protected 10-desacetyl baccatin III (10-DAB), followed by deprotection.[2] Remarkably, this structural modification induced a significant enhancement of potency in comparison with the parent drug in certain tests (inhibition activity in microtubule depolymerization and cytotoxicity toward KB-V1). This encouraging result prompted us to continue to probe the sensitive C-2′ position with the introduction of a hydroxymethyl group. Reported here is the preparation of the C-2′ hydroxymethyl derivative of docetaxel **4** (Scheme 2) and its C-2′ diastereomer *via* the use of an effective new synthetic equivalent of an asymmetric Baylis–Hillman reaction.

The C-2′ hydroxymethyl analogue of docetaxel **4**, it seemed, might be secured by vicinal dihydroxylation of the corresponding (3*S*)-3-(*N*-*tert*-butoxycarbonylamino)-2-methylene-3-phenylpropanoate,† itself most likely obtainable by esterification of protected 10-DAB with acid **3** (Scheme 2). The major advantages of such a strategy would be that steric problems in the esterification could be minimized and protecting group-related manipulations of the side chain obviated.

It was hoped that the enantiopure acid could be secured *via* a



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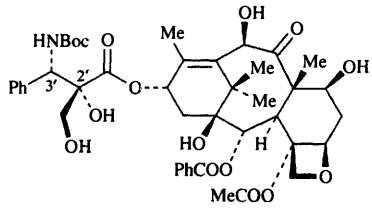
10-DAB (protected)



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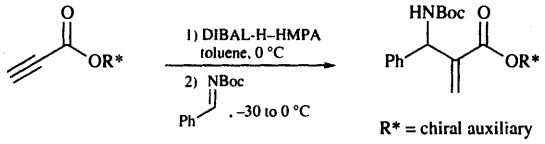
Scheme 2

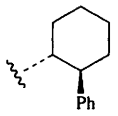
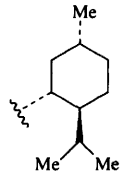
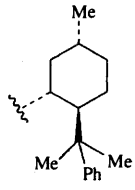
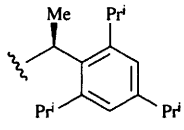
new process that would be equivalent to an asymmetric Baylis–Hillman reaction. The 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalysed reaction of an acrylate with an imine,[3] an extension of the original Baylis–Hillman reaction between an acrylate and an aldehyde,[4] represents a simple route to racemic α-(aminoalkyl)acrylate derivatives. Unfortunately, however, the development of an asymmetric version of these Baylis–Hillman reactions is made difficult by the relatively elevated reaction temperatures that are typically necessary. For example, use of a chiral acrylate[5] or a chiral C_2-symmetric catalyst[6] leads to only low asymmetric induction in the resulting α-(hydroxyalkyl)-acrylates. While high pressure with a chiral alcohol-derived acrylate has been reported to afford complete diastereoselection, it is to the detriment of the yield.[7] Also of interest, but limited in scope, is the particular case of *ortho*-substituted aryl aldehydes and imines, which have been shown to undergo, *via* their $Cr(CO)_3$ chiral complexes, efficient asymmetric Baylis–Hillman reactions.[8] Other Baylis–Hillman related processes, involving α,β-unsaturated ketones, proceed with various degrees of selectivity.[9]

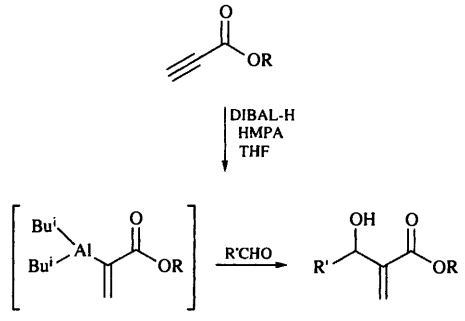
In searching for a general, efficient asymmetric route to α-(aminoalkyl)acrylate derivatives, an extension of the [α-(alkoxycarbonyl)vinyl]aluminium-mediated reaction between an alkyl propiolate and an aldehyde was considered (Scheme 3). This reaction, first reported by Tsuda *et al.*,[10] involves conjugate reduction of the acetylenic ester by hexamethylphosphoramide (HMPA)-complexed DIBAL-H, and provides generally excellent results. For use in the present context, however, it was necessary that the reaction also be applicable to imines and, more open to uncertainty, asymmetric induction prove feasible.

† For coherence with the Taxol/Taxotere side chain, this substance and related compounds are named as phenylpropanoic acid derivatives.

Table 1 Diastereoselective synthesis of α-(aminoalkyl)acrylate derivatives from chiral propiolates



R*	Yield (%)	De(%)
	90	86
	65	40
	81	40
	70	46



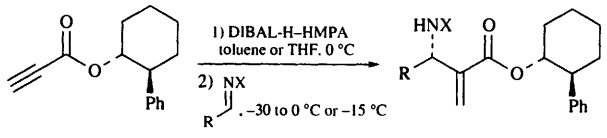
Scheme 3

It was found that propiolic acid could be efficiently esterified *via* an improved procedure with *trans*-2-phenylcyclohexanol [dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), toluene, −30 °C, 15 h] to afford in 84% yield the expected propiolate.‡ The same procedure could also be used with the much less reactive 1-(2,4,6-triisopropylphenyl)ethanol, but provided the corresponding ester in considerably reduced yield. The known menthyl[11] and 8-phenylmenthyl[12] propiolates were prepared according to the literature. Pleasingly, the vinylaluminium species resulting from hydroalumination of these propiolates were found to react smoothly with readily available benzaldehyde *N*-(*tert*-butoxycarbonyl)imine[13] to afford in the optimized procedure (1.5 equiv. of DIBAL-H, 5.7 equiv. of HMPA, toluene, 0 °C, 1.5 h, then 2.5 equiv. of the imine, −30 to 0 °C, 18 h) the desired α-(aminoalkyl)acrylate derivatives in 65 to 90% yield. As can be seen from the results given in Table 1, *trans*-2-phenylcyclohexanol (>85% de) was clearly the most effective chiral controller in this comparison.§

With benzaldehyde *N*-benzoylimine and benzaldehyde *N*-(toluene-*p*-sulfonyl)imine, this same auxiliary again provided good yields, but now outstanding diastereoselections (95:5 and >99:1, respectively). Furthermore, on reaction with the *N*-(toluene-*p*-sulfonyl)imines derived from furfuraldehyde, 2,2-dimethylpropanal and 2-naphthaldehyde,¶ the *trans*-2-phenylcyclohexyloxycarbonyl-substituted vinylaluminium intermediate also generated diastereoselections better than 95:5 (Table 2). A single crystal X-ray analysis of the major *N*-benzoyl derivative showed that (1*R*,2*S*)-2-phenylcyclohexanol induces the *S* configuration at C-3 (Fig. 1). Through chemical correlation, it could be determined that reactions with benzaldehyde *N*-(*tert*-butoxycarbonyl)imine and benzaldehyde *N*-(toluene-*p*-sulfonyl)imine, and presumably the others, also give rise to the *S* configuration at C-3 with this inductor.

Because of the facility with which acrylates undergo conjugate addition of nucleophiles and the sensitivity of the Boc group to acid, the conversion of (1′*R*,2′*S*,3*S*)-2′-phenylcyclohexyl 3-(*N*-*tert*-butoxycarbonylamino)-2-methylene-3-phenylpropanoate to its free acid was expected, and indeed proved, to

Table 2 Diastereoselective synthesis of α-(aminoalkyl)acrylate derivatives from (1′*R*,2′*S*)-phenylcyclohexyl propiolate



R	X	Yield (%)	De (%)
Ph	Boc	90	86
Ph	Bz	71	90
Ph	Ts	64	>98
Furfuryl	Ts	34	92
Bu′	Ts	73	94
2-Naphthyl	Ts	64	96

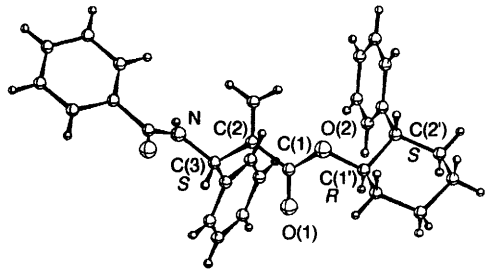


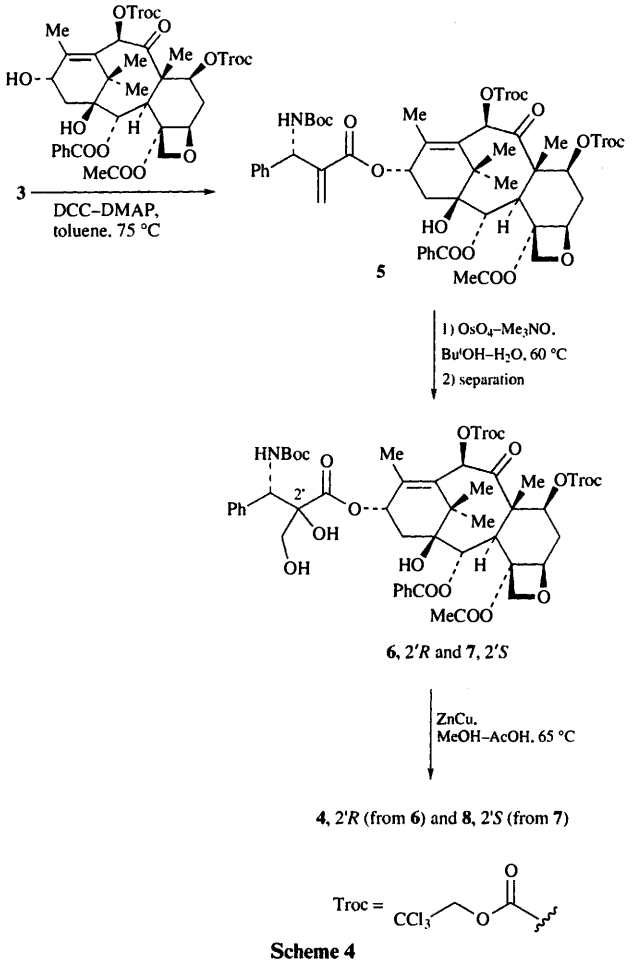
Fig. 1 Crystal structure of (1′*R*,2′*S*,3*S*)-2′-phenylcyclohexyl 3-(*N*-benzoylamino)-2-methylene-3-phenylpropanoate

‡ The originally reported conditions furnished this ester in only 40% yield (L. Balas, B. Jousseaume and B. Langwost, *Tetrahedron Lett.*, 1989, **30**, 4525). Toluene-*p*-sulfonic acid-catalysed esterification of propiolic acid with *trans*-2-phenylcyclohexanol in refluxing benzene proceeded in only 10% yield (ref. 11).

§ Although reactive (70–80% yields), aldehydes behaved quite differently: 8-phenylmenthyl propiolate gave 52% de with benzaldehyde (but des only in the 40% range were observed with the three other auxiliaries studied). Noteworthy, however, was the case of *p*-nitrobenzaldehyde, which gave 70% de (93% yield) with *trans*-2-phenylcyclohexyl propiolate. Alternative procedures for effecting this type of transformation are currently being studied.

¶ Due to the insolubility of these *N*-(toluene-*p*-sulfonyl)imines in toluene at −30 °C and their diminished reactivity, they were used in large excess (3.5 equiv.) in THF at −15 °C.

be problematical. After considerable experimentation, however, it was found that this ester, readily obtained diastereomerically pure in 67% yield by recrystallization, could be saponified (LiOH, THF–H_2O, 70 °C, 48 h) to give the corresponding enantiopure acrylic acid **3** (70%), together with the ejected inductor.‖ In the presence of DCC and DMAP in warm toluene solution for 72 h, the acid underwent smooth coupling with the 7,10-bis(trichloroethoxycarbonyl) derivative of 10-DAB to



Scheme 4

provide, in 83% yield, ester **5** (Scheme 4). On treatment with a catalytic amount of OsO_4 and excess trimethylamine *N*-oxide, the double bond of this acrylate suffered vicinal dihydroxylation to give a separable 70:30 mixture of diols **6** and **7** in 82% combined yield.**

Deprotection of the C-7 and C-10 hydroxy groups in **6** and **7** under the usual conditions proceeded uneventfully to yield the targeted diastereomeric docetaxel analogues **4** and **8**, respectively, each in *ca.* 70% yield. Interestingly, neither of these novel derivatives showed significant cytotoxicity toward KB or KB-V1. However, the major diastereomer displayed inhibitory activity in microtubule depolymerization substantially greater than that of the minor (albeit less than that shown by paclitaxel). In that it is established that the 2'*R*,3'*S* (*threo*) isomer is more active than the 2'*S*,3'*S* (*erythro*) in a given pair, the major diastereomer can be assigned with reasonable confidence the natural 2'*R*,3'*S* stereochemistry, as shown in structure **4**.

That these molecules are apparently devoid of useful biological activity may reflect significant conformational changes resulting from the introduction of the polar hydroxymethyl group (*vs.* Me or H). The new asymmetric α-(aminoalkyl)-acrylate synthesis disclosed in this paper is currently being used to prepare other modified side chains to probe this issue.

Experimental

(1'*R*,2'*S*,3*S*)-2'-Phenylcyclohexyl 3-(*N*-*tert*-butoxycarbonylamino)-2-methylene-3-phenylpropanoate

To a solution of HMPA (1.4 cm^3, 8.0 mmol) in anhydrous toluene (15 cm^3) at 0 °C under argon was added DIBAL-H (2.6 cm^3 of a *ca.* 1 M solution in hexane, 2.6 mmol). The resulting solution was stirred for 30 min, after which a solution of (1'*R*,2'*S*)-2'-phenylcyclohexyl propiolate (400 mg, 1.75 mmol) in anhydrous toluene (10 cm^3) was added. The reaction mixture was stirred at 0 °C for 1.5 h and then cooled to −30 °C and treated with a solution of freshly prepared benzaldehyde *N*-(*tert*-butoxycarbonyl)imine (1.00 g, 4.87 mmol) in toluene (10 cm^3). After being stirred at −30 °C for 16 h the reaction mixture was allowed to warm to 0 °C over 2 h and was quenched by addition of 2 M HCl. The organic layer was diluted with diethyl ether and washed with saturated aqueous sodium hydrogen carbonate. The crude product, obtained by standard treatment of the organic phase, was purified by silica gel column chromatography with 7% ethyl acetate in hexane to afford the two diastereomers as a 93:7 mixture (685 mg, 90%). Recrystallization (hexane) gave the pure major diastereomer (510 mg, 67%) as white crystals, mp 117–118 °C (hexane) (Found: C, 74.44; H, 7.76; N, 3.35. $C_{27}H_{33}O_4N$ requires C, 74.46; H, 7.64; N, 3.22%); $[\alpha]_D$ −18 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3428, 3031, 2927, 2865, 1728, 1713, 1505, 1368, 1272 and 1172; δ_H(200 MHz) 0.77–2.05 (17 H, m), 2.62 (1 H, td, *J* 11.6 and 3.7), 4.89 (1 H, td, *J* 10.6 and 4.0), 5.26 (1 H, m), 5.46 (1 H, m), 5.65 (1 H, s), 6.00 (1 H, s) and 6.90–7.40 (10 H, m); δ_C(50.3 MHz) 24.6, 25.7, 28.4, 31.9, 33.5, 49.7, 56.1, 76.6, 76.8, 125.6, 126.4, 127.2, 127.4, 128.2, 128.4, 140.2, 142.7, 154.8 and 164.9; *m/z* (IC) 436 (MH^+), 380 (100%) and 336.

(3'*R*)- and (3'*S*)-2'-Hydroxymethyl derivatives of docetaxel (4 and 8)

Lithium hydroxide (424 mg, 10.1 mmol) was added to a solution of the above acrylate (110 mg, 0.25 mmol) in THF–H_2O (4:1 v/v, 5.0 cm^3) and the resulting mixture was heated at 65–70 °C for 48 h. The reaction mixture was allowed to cool to 20 °C and, following extraction of the chiral auxiliary, the carboxylic acid **3** (50 mg, 70%) was isolated in the usual way as a pale yellow powder (Found: C, 65.15; H, 7.11; N, 4.93. $C_{15}H_{19}O_4N$ requires C, 64.97; H, 6.91; N, 5.05%); $[\alpha]_D$ +14 (*c* 1.0 in $CHCl_3$).

A solution of acid **3** (109 mg, 0.39 mmol) and DCC (81 mg, 0.39 mmol) in anhydrous toluene (6.5 cm^3) was warmed to 75 °C and 7,10-bis(trichloroethoxycarbonyl)-protected 10-DAB (117 mg, 0.13 mmol) and DMAP (19 mg, 0.16 mmol) were added in one portion. After being heated at 75 °C under argon for 70 h, the reaction mixture was allowed to cool to 20 °C and the crude product was isolated with dichloromethane in the usual manner and purified by preparative silica gel thin layer chromatography (TLC) with 3% diethyl ether in dichloromethane to afford the acrylate **5** (126 mg, 83%) as a white foam (Found: C, 52.20; H, 4.97; N, 1.54. $C_{50}H_{55}O_{17}NCl_6$ requires C, 52.00; H, 4.80; N, 1.21%); $[\alpha]_D$ −27 (*c* 1.0 in $CHCl_3$).

To a solution of acrylate **5** (97.7 mg, 0.085 mmol) in Bu'OH–H_2O (4:1 v/v, 1.0 cm^3) were added successively trimethylamine *N*-oxide (10 mg, 0.09 mmol) and osmium tetroxide (0.053 cm^3 of a 2.5% w/w solution in Bu'OH, 0.004 mmol). The reaction mixture was then heated at 60 °C for 1 h, after which it was allowed to cool to 20 °C. Sodium hydrogen sulfite (150 mg) in water (2 cm^3) was added and the mixture was stirred at 20 °C for

‖ This procedure could also be applied to the α-(hydroxyalkyl)acrylate resulting from the reaction between benzaldehyde and *trans*-2-phenylcyclohexyl propiolate.

** When a stoichiometric amount of OsO_4 was used in pyridine, the dihydroxylation proceeded in lower yield (66%), but with greater selectivity (80:20).

30 min. The crude product mixture, isolated with ethyl acetate in the usual way, was separated by preparative silica gel TLC with 1% methanol in dichloromethane to afford the pure diols **6** and **7**. Major diastereomer **6** (57.6 mg, 57%) (Found: C, 50.61; H, 5.12; N, 1.52. $C_{50}H_{57}O_{19}NCl_6$ requires C, 50.52; H, 4.83; N, 1.18%); $[\alpha]_D$ −31 (*c* 1.0 in $CHCl_3$). Minor diastereomer **7** (25.7 mg, 25%) (Found: C, 49.92; H, 5.28; N, 1.32. $C_{50}H_{57}O_{19}N$-$Cl_6 \cdot 1H_2O$ requires C, 49.77; H, 4.93; N, 1.16%); $[\alpha]_D$ −23 (*c* 1.0 in $CHCl_3$).

Zinc–copper couple (290 mg, 4.43 mmol) was added to a solution of the major diastereomer **6** (58.5 mg, 0.049 mmol) in methanol–acetic acid (1:1 v/v, 7.2 cm^3) at 65 °C. After being vigorously stirred at this temperature for 1.5 h, the reaction mixture was allowed to cool to 20 °C, diluted with dichloromethane and filtered through Celite. The crude product was extracted with dichloromethane in the usual manner and purified by preparative silica gel TLC with 10% methanol in dichloromethane to afford the derivative **4** (29 mg, 70%), $[\alpha]_D$ −37 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3452, 2984, 2940, 1713, 1498, 1372, 1248, 1165 and 1069; δ_H(200 MHz) 1.11 (3 H, s) 1.23 (9 H, s), 1.26 (3 H, s), 1.75 (3 H, s) 1.50–1.90 (2 H, m), 2.10–2.35 (1 H, m), 2.34 (3 H, s), 2.40–2.70 (1 H, m), 2.60 (3 H, s), 3.65 (2 H, AB q, J_{AB} 10.8, δ_A–δ_B 61.2), 3.90 (1 H, d, *J* 6.9), 4.10–4.30 (1 H, m), 4.24 (2 H, AB q, J_{AB} 8.4, δ_A–δ_B 24.8), 4.96 (1 H, d, *J* 8.6), 5.09 (1 H, d, *J* 10.3), 5.17 (1 H, s), 5.61 (1 H, d, *J* 10.6), 5.66 (1 H, d, *J* 7.2), 6.35 (1 H, t, *J* 8.6), 7.20–7.70 (8 H, m) and 8.07–8.12 (2 H, m); δ_C(62.5 MHz) 10.0, 13.8, 14.1, 21.0, 21.3, 22.9, 26.5, 28.1, 29.6, 35.9, 36.7, 43.1, 46.3, 53.4, 56.2, 57.5, 60.4, 65.6, 71.8, 72.3, 74.3, 74.9, 76.6, 79.2, 80.0, 81.0, 81.3, 84.3, 128.0, 128.2, 128.5, 128.7, 129.1, 130.2, 133.6, 135.2, 137.3, 139.1, 154.9, 167.1, 170.7, 171.3, 174.0 and 211.2; *m/z* (FAB^+) 838 (MH^+) [Found: $(M + Li)^+$, 844.3732. $C_{44}H_{55}O_{15}NLi$ requires *M*, 844.3727].

In the same way the minor diastereomer **7** (50 mg, 0.042 mmol) was converted to analogue **8** (25 mg, 71%), $[\alpha]_D$ −66 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3454, 2975, 2935, 1702, 1495, 1368, 1266, 1164, 1120 and 1066; δ_H(200 MHz) 1.17 (3 H, s), 1.24 (3 H, s), 1.42 (9 H, s), 1.69 (3 H, s), 1.74 (3 H, s), 1.50–1.90 (3 H, m), 2.15 (3 H, s), 2.40–2.70 (1 H, m), 3.70 (1 H, d, *J* 7.2), 3.82 (1 H, d, *J* 10.6), 4.00–4.40 (4 H, m), 4.86 (1 H, d, *J* 8.6), 5.06–5.12 (2 H, m), 5.52 (1 H, d, *J* 7.5), 5.62 (1 H, d, *J* 10.6), 6.11 (1 H, t, *J* 8.7), 7.05–7.75 (8 H, m) and 7.95–8.03 (2 H, m); δ_C(62.5 MHz) 9.9, 14.1, 14.4, 21.0, 22.3, 22.6, 26.5, 28.3, 31.6, 35.3, 36.8, 42.9, 46.3, 56.4, 57.4, 60.4, 67.3, 71.0, 71.9, 74.3, 74.8, 79.0, 80.3, 80.9, 82.7, 84.1, 128.3, 128.6, 129.3, 130.1, 133.8, 135.1, 138.8, 155.4, 166.8, 171.7, 172.8 and 211.1; *m/z* (FAB^+) 838 (MH^+) [Found: $(M + H)^+$, 838.3656. $C_{44}H_{56}O_{15}N$ requires *M*, 838.3650].

Crystal data for (1′*R*,2′*S*,3*S*)-2′-phenylcyclohexyl 3-(*N*-benzoylamino)-2-methylene-3-phenylpropanoate

$C_{29}H_{29}NO_3$, $M = 439.53$. Monoclinic, $a = 14.707(9)$, $b = 10.325(6)$, $c = 17.691(9)$ Å, $\beta = 113.79(5)°$, $V = 2458(2)$ $Å^3$, $Z = 4$, $D_x = 1.188$ g cm^{-3}, space group $P2_1/n$ (alt. $P2_1/c$, No. 14), Colourless needles crystallized from diethyl ether, 0.10 × 0.20 × 0.35 mm. The crystal was mounted on a Nicolet XRD four circle diffractometer using a graphite crystal monochromator [λ(Mo-Kα) = 0.710 73 Å]. 3693 reflections were collected at 293 K in a range $3 \leq 2\theta \leq 50°$, and were corrected for Lorentz and polarization effects but not for absorption ($\mu = 0.076$ mm^{-1}). 3577 independent reflections were used in the structural analysis. The structure was solved by direct methods (SHELXS-86)[14] and refined against all F^2 (SHELXL-93).[15] All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms [N(H), C(3)H, C(1′)H and C(2′)H] of nitrogen (N) and asymmetric carbons (C-3, C-1′ and C-2′) were localized on a difference Fourier map and were refined with isotropic thermal parameters. The others were generated in idealized positions and refined, riding on the carrier atoms, with isotropic thermal parameters $U(H) = 1.2\ U_{eq}(C)$. Final cycle refinement, including 314 parameters, converged to $R(F) = 0.062$ [for 1858 $F > \sigma(F)$]; $wR(F^2) = 0.1666$ for all 3577 F^2[$(\Delta/\sigma)_{max} = 0.006$, $\Delta\rho_{max} = 0.14$ e $Å^{-3}$, $\Delta\rho_{min} = -0.19$ e $Å^{-3}$, no extinction correction].

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/72.

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