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Central-to-axial chirality transfer and induced circular dichroism in 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine derivatives of α- and β-amino esters

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Abstract

DAZ-Xaa*-OMe amino ester derivatives with Xaa* = D/L-Ala, D/L-Val, L-Leu, L-Ile, L-Ser, L-β³-HAla, L-β³-HVal, L-β³-HLeu, (1*S*,2*S*)/(1*R*,2*R*)-ACHC (2-aminocyclohexanecarboxylic acid) and (1*S*,2*S*)/(1*R*,2*R*)-ACPC (2-aminocyclopentanecarboxylic acid), *N*-blocked as 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines (DAZ), have been synthesized and evaluated for the determination of the absolute configuration of α- and β-amino esters through the induced circular dichroism of the biphenyl chromophore.

Keywords: Atropisomerism; Absolute configuration; α- and β-Amino acids; Biphenyl; Induced axial chirality; Induced circular dichroism

Transfer of central-to-axial chirality in conformationally flexible biphenyl systems results in an induced circular dichroism (ICD)[1] of the biphenyl chromophore, which has been used as a tool for the determination of the absolute configuration of chiral 1,2- and 1,3-diols by means of biphenyldioxolane derivatives[2] and of chiral secondary alcohols in dinitrodiphenic esters.[3] In our groups, by taking advantage of the presence of a flexible biphenyl probe in 2′,1′:1,2;1″,2″:3,4-dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid (Bip), we proposed the '*Bip method*' for an easy and fast configurational assignment of chiral α- and β-Xaa* amino acids, based on the ICD observed in the terminally protected Boc-Bip-α-Xaa*-OMe[4] as well as Boc-Bip-β-Xaa*-OMe[5] dipeptides. More recently, Rosini and co-workers[6] have reported a very interesting method for the determination of the absolute configuration of *N*-Boc protected α-amino acids (and carboxylic acids as well) from ICD of their 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine amide derivatives **A** (Fig. 1), in which central chirality of an aliphatic (*S*)-α-amino acid or organic acid induces a preferential (*P*) torsion of the flexible biphenyl probe and gives rise to a negative Cotton effect at 250 nm (A band). At the same time, we were interested in the investigation of a central-to-axial chirality transfer in related derivatives

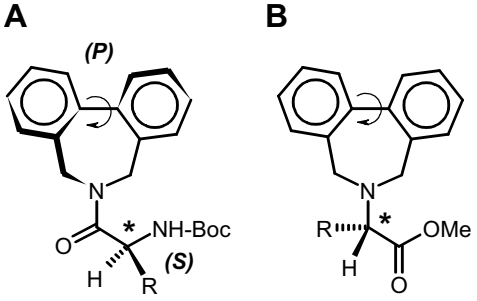

Fig. 1. Chemical structures of 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine amide derivatives of *N*-Boc protected α-amino acids (**A**),[6] and of α-amino esters *N*-blocked as 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine derivatives (**B**).

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of type **B**, in which α-amino esters (as well as β^3- and cyclic β-amino esters) are *N*-blocked as 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines [*Note*: in the following sections, we have used the term 'DAZ' for such blocked amino groups]. Here, we report the syntheses, and ^{1}H NMR and CD analyses of a series of DAZ-Xaa*-OMe amino esters with Xaa* = D/L-Ala, D/L-Val, L-Leu, L-Ile, L-Ser, L-β^3-HAla, L-β^3-HVal, L-β^3-HLeu, (1*S*,2*S*)/(1*R*,2*R*)-ACHC, and (1*S*,2*S*)/(1*R*,2*R*)-ACPC (Fig. 2).

The DAZ-Xaa*-OMe derivatives were readily obtained by the reaction of 2,2′-bis(bromomethyl)-1,1′-biphenyl with the amino esters H-Xaa*-OMe (Fig. 2) in THF (tetrahydrofuran) at 60 °C in the presence of an excess of DIEA (diisopropylethylamine). The derivatives DAZ-L/D-Ala-OMe, DAZ-L/D-Val-OMe, DAZ-L-Leu-OMe, DAZ-L-Ile-OMe, DAZ-L-Ser-OMe, DAZ-L-β^3-HAla-OMe, DAZ-L-β^3-HVal-OMe, DAZ-L-β^3-HLeu-OMe, DAZ-(1*S*,2*S*)/(1*R*,2*R*)-ACHC and DAZ-(1*S*,2*S*)/(1*R*,2*R*)-ACPC (Fig. 2) were isolated in moderate to high yield (21–97%).[7] The ease of this double N-derivatization of amino esters relies on the exclusive formation of the seven-membered ring system in the reaction of primary or secondary amines with this dibromide, established in the 1950s[8] and exploited by several authors.[9]

The conformational equilibrium between the two diastereoisomeric conformers, resulting from the concomitant presence of chiral centre(s) in the Xaa* amino esters and (*P*) and (*M*) torsions of the biphenyl group (Fig. 2), was established by ^{1}H NMR analysis of the DAZ-Xaa*-OMe derivatives in CD_3OD solution at low temperature. For all the compounds, while sharp signals were generally observed at 293 K under fast interconverting conditions, broadening occurred with decreasing temperature. In particular, at ca. 203 K two sets of signals were seen, corresponding to the presence of two diastereoisomers with unequal populations exchanging slowly on the NMR time scale. As an illustration, the evolution of the ^{1}H NMR spectrum of DAZ-L-Leu-OMe as a function of temperature is shown in Figure 3. For this compound, according to the chemical shift difference between the –COOMe methoxy singlets of the two conformers at 203 K ($\Delta\nu = 51.1$ Hz; Table 1) and the corresponding coalescence temperature ($T_C \sim 230$ K; Fig. 3), the calculated[10] rotational energy barrier of the biphenyl moiety was ca. 11 kcal mol^{-1}.

The diastereoisomeric ratio (d.r.) was determined at 203 K by integration of the best separated sets of signals. The singlet due to the –COOMe group was especially suitable for this purpose, since for all the derivatives, except DAZ-L-β^3-HAla-OMe, the singlets corresponding to this group for both diastereoisomers appeared at different chemical shifts (Table 1). However, in some cases, partial overlapping between the –COOMe singlets and the complicated signal patterns due to the $ArCH_2N$ protons of the DAZ moiety prevented precise measurements. In any case, only low d.r. values, ranging from ca. 50:50 to 66:34, were observed for the DAZ-Xaa*-OMe derivatives of α-, β^3- and cyclic β-amino esters (Table 1).

The biphenyl chromophore is characterized by an intense electronic absorption at about 240–250 nm, assigned to the A band,[11] followed by a very intense transition at ca. 210–215 nm (C band). It has been well established that in the CD spectra of biphenyl-based chiral molecules a positive maximum corresponding to the A band is related to a (*M*) torsion of the C_{Ar}–C_{Ar} bond.[12–14] CD analyses in MeOH (methanol) solution of all of the DAZ-Xaa*-OMe derivatives listed in Figure 2 were carried out. The spectra indicate that, as expected, an ICD resulting from the axial chirality in the biphenyl

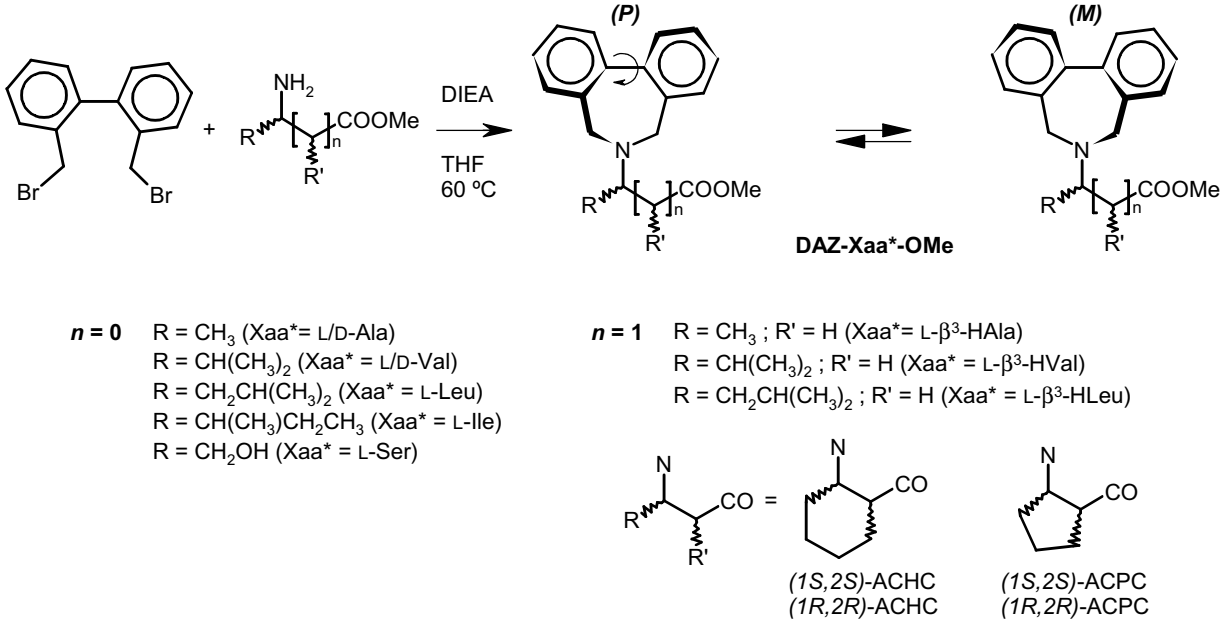

Fig. 2. Synthesis, chemical structures and diastereoisomer equilibrium of the DAZ-Xaa*-OMe amino esters discussed in this work.

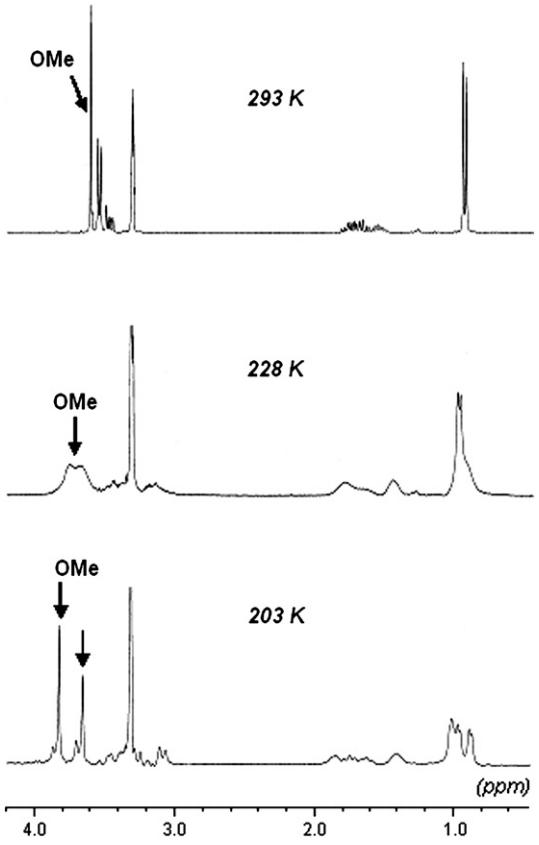

Fig. 3. Temperature-dependent ^{1}H NMR spectra of DAZ-L-Leu-OMe in CD_3OD solution at 203 K (the arrows indicate the separation of the –COOMe singlet in both diastereoisomeric conformers), 228 K (close to coalescence), and 293 K (fast exchange).

Table 1
Chemical shifts δ (ppm) of the –COOMe singlet(s) at 293 K and 203 K for the DAZ-Xaa*-OMe derivatives in CD_3OD solution, and calculated diastereoisomeric ratios (d.r.) at 203 K

DAZ-amino esters	δ (–COOMe) ppm		d.r.
	293 K	203 K	
DAZ-L-Ala-OMe	3.70	3.81, 3.70	66:34
DAZ-L-Val-OMe	3.53	3.74, 3.55	50:50
DAZ-L-Ile-OMe	3.55	3.78, 3.58	58:42
DAZ-L-Leu-OMe	3.60	3.82, 3.65	58:42
DAZ-L-Ser-OMe	3.65	3.80, 3.69	—[a]
DAZ-L-β^3-HAla-OMe	3.68	3.67	—[a]
DAZ-L-β^3-HVal-OMe	3.61	3.74, 3.70	—[a]
DAZ-L-β^3-HLeu-OMe	3.65	3.67, 3.63	53:47
DAZ-(1*S*,2*S*)-ACPC-OMe	3.70	3.83, 3.59	53:47
DAZ-(1*S*,2*S*)-ACHC-OMe	3.66	3.74, 3.62	62:38

[a] Not measured because of signal overlapping.

core of DAZ induced by the chiral carbon centre is generally observed. More specifically, the following points may be highlighted:

(i) Comparison of the CD spectra of DAZ-L-Ala-OMe, DAZ-L-Val-OMe, DAZ-L-Ile-OMe, DAZ-L-Leu-OMe, and DAZ-L-Ser-OMe (Fig. 4 and Table 2),

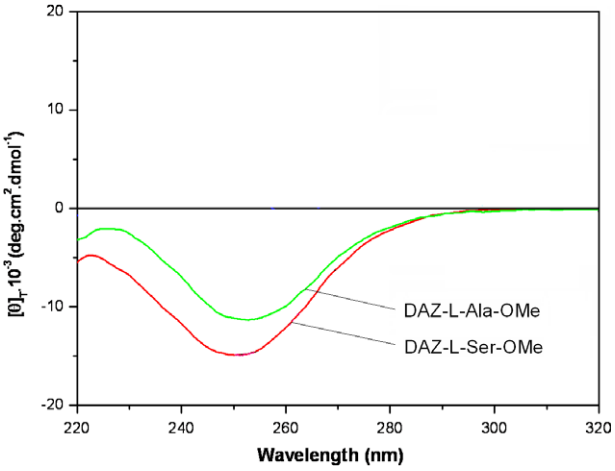

Fig. 4. CD spectra (220–320 nm range) of selected DAZ-L-α-Xaa*-OMe derivatives in MeOH solution (DAZ-amino ester concd 1 mM).

Table 2
Position λ (nm), intensity, and sign of the A band, correlated with (*P*) or (*M*) torsion of the biphenyl core, for the DAZ-Xaa*-OMe derivatives in MeOH solution

DAZ amino ester	Cotton effect (A band)			Central asymmetry	Biphenyl torsion
	λ(nm)	Intensity[a]	Sign		
DAZ-L-Ala-OMe	253.0	12	(−)	(*S*)	(*P*)
DAZ-D-Ala-OMe	253.0	12	(+)	(*R*)	(*M*)
DAZ-L-Val-OMe	261.0	1	(−)	(*S*)	(*P*)
DAZ-D-Val-OMe	261.0	0.5	(+)	(*R*)	(*M*)
DAZ-L-Ile-OMe	258.3	5	(−)	(*S*)	(*P*)
DAZ-L-Leu-OMe	254.1	3	(−)	(*S*)	(*P*)
DAZ-L-Ser-OMe	250.7	15	(−)	(*S*)	(*P*)
DAZ-L-β^3-HAla-OMe	250.5	3	(−)	(*S*)	(*P*)
DAZ-L-β^3-HVal-OMe	250.5	8	(−)	(*R*)[b]	(*P*)
DAZ-L-β^3-HLeu-OMe	244.0	1	(−)	(*S*)	(*P*)
DAZ-(1*S*,2*S*)-ACPC-OMe	257.8	6	(+)	(1*S*,2*S*)	(*M*)
DAZ-(1*R*,2*R*)-ACPC-OMe	257.8	6	(−)	(1*R*,2*R*)	(*P*)
DAZ-(1*S*,2*S*)-ACHC-OMe	250.1	1	(+)	(1*S*,2*S*)	(*M*)
DAZ-(1*R*,2*R*)-ACHC-OMe	250.1	1	(−)	(1*R*,2*R*)	(*P*)

[a] Expressed as the total molar ellipticity $[\Theta]_T \times 10^{-3}$ (deg cm^2 dmol^{-1}).
[b] Corresponds to the same spatial arrangement as (*S*)-β^3-HAla and (*S*)-β^3-HLeu.

shows that a negative Cotton effect at ca. 250 nm, associated with a (*P*) torsion of the biphenyl axial bond, is preferentially induced by *L* [(*S*) absolute configuration] aliphatic α-amino esters. The CD spectra of the enantiomeric DAZ-L-Ala-OMe and DAZ-D-Ala-OMe are mirror images (Fig. 5), as are those of DAZ-L-Val-OMe and DAZ-D-Val-OMe (Table 2). Both the wavelength of the ICD maximum and its intensity are strongly dependent on the nature of the side chain of the α-Xaa* residue: at 250.7 nm with total molar ellipticity $[\Theta]_T \times 10^{-3}$ (deg cm^2 dmol^{-1}) = −15 for DAZ-L-Ser-OMe, at

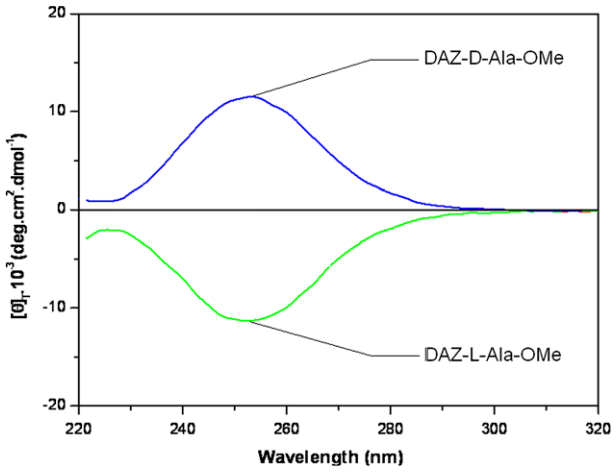

Fig. 5. CD spectra (220–320 nm range) of selected DAZ-L-/D-α-Xaa*-OMe derivatives in MeOH solution (DAZ-amino ester concd 1 mM).

253.0 nm with $[\Theta]_T \times 10^{-3} = -12$ for DAZ-L-Ala-OMe, at 258.3 nm with $[\Theta]_T \times 10^{-3} = -5$ for DAZ-L-Ile-OMe, at 254.1 nm with $[\Theta]_T \times 10^{-3} = -3$ for DAZ-L-Leu-OMe, and at 261.0 nm with $[\Theta]_T \times 10^{-3} = -1$ for DAZ-L-Val-OMe (Table 2).

(ii) The same relationship is observed for the DAZ-L-β^3-Xaa*-OMe amino esters in which a (*P*) torsion of the biphenyl axial bond (negative sign of the Cotton effect at ca. 250 nm) is also preferentially induced by an *L* [or (*S*)] configuration of the chiral carbon centre (Fig. 6 and Table 2) [*Note*: according to nomenclature, the absolute configuration of DAZ-L-β^3-HVal-OMe is in fact (*R*), but corresponds to the same spatial arrangement as L-β^3-HAla and L-β^3-HLeu]. In contrast, the correlation between the absolute configuration of the carbon bearing the amino group and the sign of the Cotton effect is reversed in the case of the cyclic β-amino esters DAZ-(1*S*,2*S*)-ACHC-OMe and DAZ-(1*S*,2*S*)-ACPC-OMe, which present an ICD with a positive Cotton effect of the A band. The CD spectra of their enantiomers DAZ-(1*R*,2*R*)-ACHC-OMe and DAZ-(1*R*,2*R*)-ACPC-OMe, respectively, are mirror images of the former (Fig. 7 and Table 2). Altogether, for acyclic as well as cyclic β-amino esters, both the wavelength of the ICD maximum and its intensity are strongly dependent on the molecular structure of the β-Xaa* residue, as observed in the α-Xaa* series.

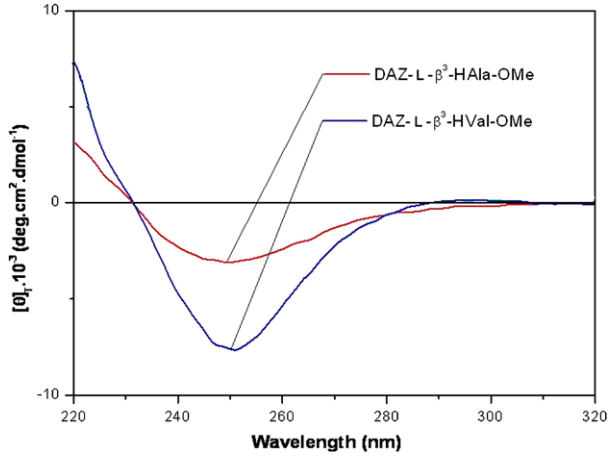

Fig. 6. CD spectra (220–320 nm range) of selected acyclic DAZ-L-β^3-Xaa*-OMe derivatives in MeOH solution (DAZ-amino ester concd 1 mM).

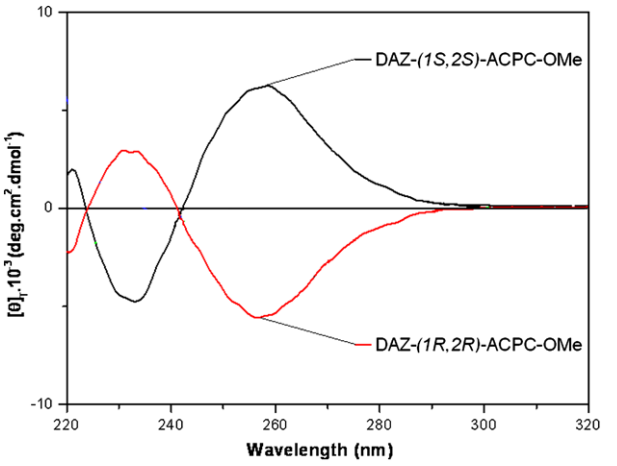

Fig. 7. CD spectra (220–320 nm range) of selected cyclic DAZ-β-Xaa*-OMe derivatives in MeOH solution (DAZ-amino ester concd 1 mM).

In summary, a significant central-to-axial induction of chirality has been revealed by both NMR and CD techniques, in a series of α- and β-amino ester derivatives DAZ-Xaa*-OMe, N-blocked as 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines. However, the relationship between the ICD and the absolute configuration of the amino ester cannot as yet be rationalized, since both α- and β-L-Xaa* acyclic residues preferentially induce a (*P*) torsion in the biphenyl chromophore (negative ellipticity at 250 nm), while cyclic β-amino esters (ACPC and ACHC), characterized by the same (*S*) absolute configuration at their β-carbon atom, show a positive Cotton effect of the A band, corresponding to a (*M*) torsion. Furthermore, both the wavelength of the ICD maximum and its intensity are generally strongly dependent on the molecular structure of the amino ester. More information on the factors governing the ICD is needed for the use of DAZ-Xaa*-OMe derivatives as spectroscopic probes for the determination of the absolute configuration of α-, β^3- and cyclic β-amino esters. In particular, as these effects might be related to different torsion angles of the biphenyl moiety, restricting the mobility of the seven-membered ring containing the tertiary amino group of DAZ seems to be of significant interest. Consequently, further DAZ derivatives of amino esters, chiral amines, and amino alcohols, conformationally restricted either by N-protonation or N-alkylation, will be synthesized in our groups for comparative evaluation of their CD spectra.

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7. *Selected analytical data*: All DAZ-amino esters gave satisfactory analytical data (^{1}H NMR, ^{13}C NMR, ESI$^+$/MS and C, H, N analysis). (1) *DAZ*-D-*Ala*-*OMe*: $R_f = 0.60$ (CH_2Cl_2–MeOH 95:5). ^{1}H NMR (CD_3OD): δ 1.42 (d, $J = 6.9$ Hz, 3H, CH_3^{β}), 3.45 (m, 1H, CH^{α}), 3.47 and 3.52 [(d, $J = 12.5$ Hz, 2H) and (d, $J = 12.5$ Hz, 2H), $ArCH_2$ DAZ], 3.70 (s, 3H, OCH_3), 7.36–7.53 (m, 8H, CH_{Ar}). ^{1}H NMR ($CDCl_3$): δ 1.45 (d, $J = 6.7$ Hz, 3H, CH_3^{β}), 3.45–3.59 (m, 5H, CH^{α} and $ArCH_2$ DAZ), 3.72 (s, 3H, OCH_3), 7.36–7.52 (m, 8H, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 16.9 (CH_3^{β}), 52.0 (OCH_3), 53.0 ($ArCH_2$ DAZ), 61.7 (CH^{α}), 127.8, 127.9, 128.3, 130.2 (CH_{Ar}), 134.6, 141.2 (C_{Ar}), 174.7 (C=O). $[\alpha]_D^{25}$ +35.6; $[\alpha]_{578}^{25}$ +37.3; $[\alpha]_{546}^{25}$ +43.9; $[\alpha]_{436}^{25}$ +90.5; $[\alpha]_{365}^{25}$ +187.9 (*c* 0.3, MeOH). MS (ESI$^+$) *m*/*z*: 282 [M+H]$^+$. Anal. Calcd for $C_{18}H_{19}NO_2$ (281.340): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.17; H, 6.68; N, 4.89. (2) *DAZ*-L-β^3-*HVal*-*OMe*: $R_f = 0.65$ (CH_2Cl_2–MeOH 95:5). ^{1}H NMR (CD_3OD): δ 0.91 (d, $J = 6.7$ Hz, 3H, CH_3^{δ}), 1.00 (d, $J = 6.6$ Hz, 3H, $CH_3^{\delta'}$), 2.02 (m, 1H, CH^{γ}), 2.46 and 2.59 [(dd, $J = 6.2$ Hz and 15.9 Hz, 1H) and (dd, $J = 5.2$ Hz and 15.8 Hz, 1H), CH_2^{α}], 3.04 (m, 1H, CH^{β}), 3.49 and 3.55 [(d, $J = 12.3$ Hz, 2H) and (d, $J = 12.3$ Hz, 2H), $ArCH_2$ DAZ], 3.62 (s, 3H, OCH_3), 7.37–7.48 (m, 8H, CH_{Ar}). ^{1}H NMR ($CDCl_3$): δ 0.94 (d, $J = 6.4$ Hz, 3H, CH_3^{δ}), 1.03 (d, $J = 6.5$ Hz, 3H, $CH_3^{\delta'}$),1.95 (m, 1H, CH^{γ}), 2.41 and 2.64 [(dd, $J = 6.9$ Hz and 15.6 Hz, 1H) and (d, $J = 15.8$ Hz, 1H), CH_2^{α}], 3.09 (m, 1H, CH^{β}), 3.52 (s, 4H, $ArCH_2$ DAZ), 3.64 (s, 3H, OCH_3), 7.38–7.50 (m, 8H, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 19.5 (CH_3^{δ}), 21.2 ($CH_3^{\delta'}$), 32.5 (CH^{γ}), 36.0 (CH_2^{α}), 51.8 (OCH_3), 52.8 ($ArCH_2$ DAZ), 68.1 (CH^{β}), 127.8, 128.0, 128.2, 130.0 (CH_{Ar}), 136.2, 141.1 (C_{Ar}), 174.3 (C=O). $[\alpha]_D^{25}$ +11.0; $[\alpha]_{578}^{25}$ +13.5; $[\alpha]_{546}^{25}$ +14.6; $[\alpha]_{436}^{25}$ +20.0 (*c* 0.3, MeOH). MS (IC$^+$) *m*/*z*: 324 [M+H]$^+$. Anal. Calcd for $C_{21}H_{25}NO_2 \cdot 0.5H_2O$(332.426): C, 75.87; H, 7.88; N, 4.21. Found: C, 75.54; H, 7.28; N, 4.17. (3) *DAZ*-(1*S*,2*S*)-*ACPC*-*OMe*: $R_f = 0.21$ (CH_2Cl_2–MeOH 95:5). ^{1}H NMR (CD_3OD): δ 1.67–2.27 (m, 6H, $CH_2^{\gamma}, CH_2^{\delta}, CH_2^{\varepsilon}$), 2.95 (m, 1H, CH^{α}), 3.43–3.54 (m, 5H, CH^{β} and $ArCH_2$ DAZ), 3.70 (s, 3H, OCH_3), 7.40–7.56 (m, 8H, CH_{Ar}). ^{1}H NMR ($CDCl_3$): δ 1.65–2.19 (m, 6H, $CH_2^{\gamma}, CH_2^{\delta}$, CH_2^{ε}), 2.98 (m, 1H, CH^{α}), 3.44 (m, 1H, CH^{β}), 3.49 (s, 4H, $ArCH_2$ DAZ), 3.72 (s, 3H, OCH_3), 7.38–7.56 (m, 8H, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 24.9 (CH^{δ}), 31.1 (CH_2^{ε}), 32.8 (CH_2^{γ}), 49.0 (CH^{α}), 51.9 (OCH_3), 53.7 ($ArCH_2$ DAZ), 67.4 (CH^{β}), 127.5, 127.8, 128.1, 129.9 (CH_{Ar}), 134.6, 141.1 (C_{Ar}), 177.4 (C=O). $[\alpha]_D^{25}$ +45.8; $[\alpha]_{578}^{25}$ +52.1; $[\alpha]_{546}^{25}$ +63.3; $[\alpha]_{436}^{25}$ +107.5 (*c* 0.2, MeOH). MS (ESI$^+$) *m*/*z*: 322.0 [M+H]$^+$. Anal. Calcd for $C_{21}H_{23}NO_2 \cdot 0.5H_2O$ (330.410): C, 76.33; H, 7.32; N, 4.23. Found: C, 76.55; H, 7.06; N, 4.17.
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