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Diastereoselective nitrilimine cycloaddition to the C=N bond of enantiopure 1,4-benzodiazepinones

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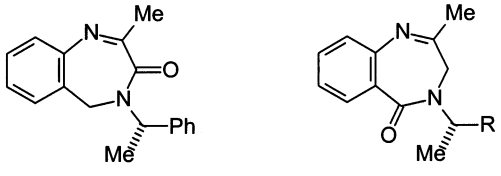
Abstract—Enantiopure 1,4-benzodiazepin-4-one **1** and 1,4-benzodiazepin-6-ones **2** were reacted with hydrazonoyl chloride **8** in the presence of various basic agents. The diastereoselective 1,3-dipolar cycloaddition between the C=N double bond of **1** or **2** and the nitrilimine intermediate **9** gave the enantiopure [1,2,4]triazolo[4,3-*a*][1,4]benzo diazepinones **10**–**13**.

1. Introduction

Due to the increasing demand for single-enantiomer pharmaceuticals and bioactive molecules, organic chemists are increasingly required to synthesise new compounds in enantiopure form rather than as racemic mixtures.[1] For instance, stereoselective 1,3-dipolar cycloaddition is now a well-established synthetic methodology which enables the construction of a variety of heterocyclic systems in enantiopure form.[2,3] Recently, our group has published several papers describing the diastereoselective cycloadditions of nitrilimines[4] and azides[5] in both the inter- and intramolecular version. It is known that the C=N bond of some benzodiazepines[6] and benzotriazepines[7] behaves as a dipolarophile toward nitrilimines, but the literature precedents are only concerned with racemic syntheses.[8] We present herein the first diastereoselective cycloaddition of nitrilimine to the C=N bond of enantiopure 1,4-benzodiazepin-4-one **1** and 1,4-benzodiazepin-6-ones **2** (Fig. 1). The resulting [1,2,4]triazolo-[4,3-*a*][1,4]benzodiazepine skeleton, obtained in non-racemic form, represents a valuable target due to its close structural similarity with the anti-anxiety agents Alprazolam,[9] Estazolam[10] and the anti-depressant Flumazenil.[11]

2. Results and discussion

The synthesis of 1,4-benzodiazepin-5-ones **2** is outlined in Scheme 1, while that of 1,4-benzodiazepin-4-one **1** was performed as previously reported by us.[5] The key step was the intramolecular cycloaddition of the alkenylazides **6** via the labile 1,2,3-triazole cycloadduct **7**, whose intervention and fate has been discussed elsewhere.[6a,12] With enantiopure **1** and **2** in hand, the subsequent step was concerned with their behaviour as dipolarophiles towards nitrilimine **9**. The generation of the latter 1,3-dipolar intermediate was accomplished in situ by treatment of the corresponding hydrazonoyl chloride **8**[13] with a suitable base in the presence of **1** or **2** (Scheme 2). The reaction times and bases, as well as product yields and diastereoisomeric ratio data, are collected in Table 1. Simple silica gel column chromatography of the reaction mixtures allows the facile separation of the pure diastereoisomeric cycloadducts **10**–**13**. Structural assignments of the above cycload-



2a: R = Ph; **2b:** R = *t*-Bu

Figure 1.

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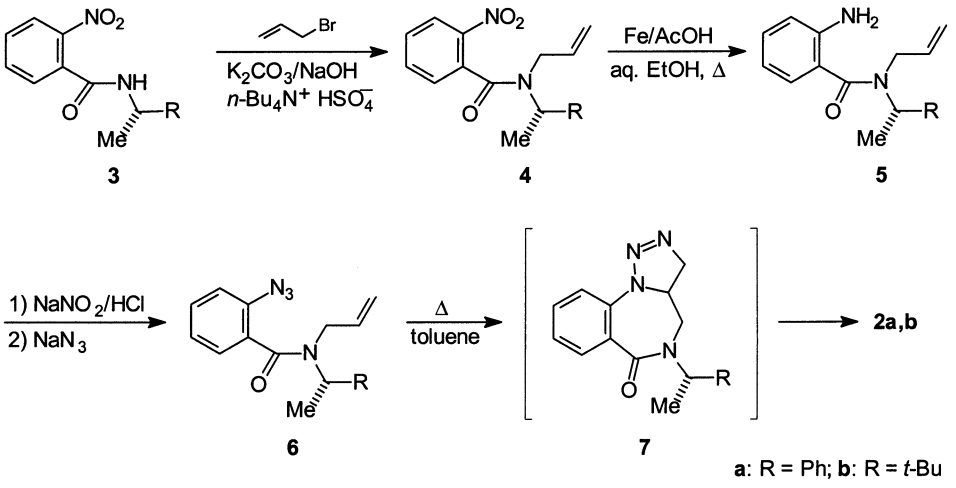
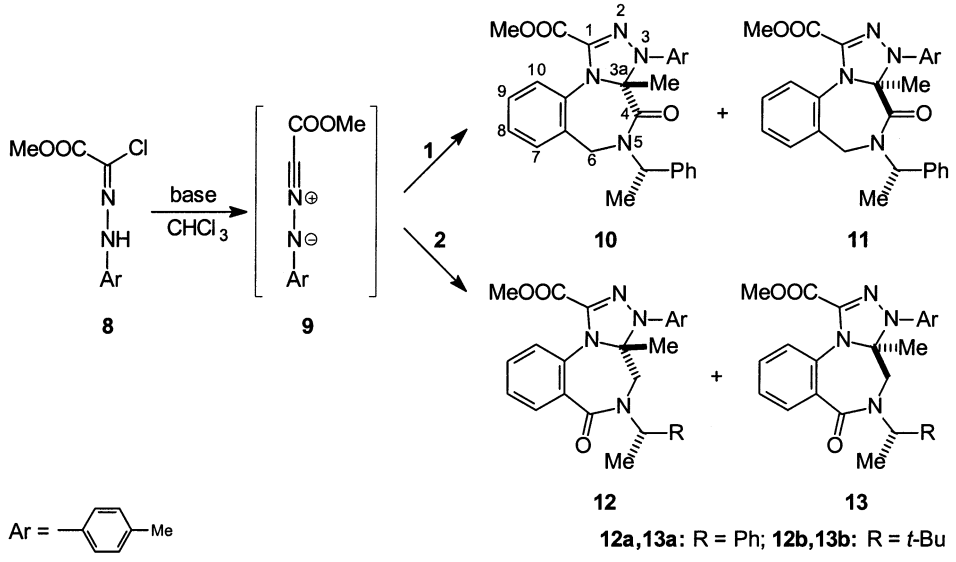


Scheme 1.



Scheme 2.

Table 1. Cycloadditions between nitrilimine **9** and enantiopure 1,4-benzodiazepinones **1** and **2** in dry chloroform[a]

Entry	Time (h)	Base (equiv.)	Products and yields (%)[b]				Product ratio[c]	
			10	**11**	**12**	**13**	**10**:**11**	**12**:**13**
1	24	Et_3N (5)	22	22	–	–	50:50	–
1	22	(−)-Sparteine (3)	36	36	–	–	50:50	–
1	3.5	AcOAg (1.5)	40	40	–	–	50:50	–
2a	48	Et_3N (5)	–	–	39	19	–	67:33
2a	16	(−)-Sparteine (3)	–	–	53	22	–	70:30
2a	6	AcOAg (1.5)	–	–	59	19	–	75:25
2b	24	Et_3N (5)	–	–	33	22	–	75:25
2b	16	(−)-Sparteine (3)	–	–	58	12	–	83:17
2b	7	AcOAg (1.5)	–	–	69	6	–	92:8

[a] At room temperature.
[b] Isolation yields.
[c] Deduced from ^1H NMR of reaction crude.

ducts rely upon analytical and spectroscopic data. As far as the ^{1}H NMR spectra are concerned, one of the cycloadducts arising from **1** show a marked upfield shift in the resonance of the aromatic hydrogen in the 7-position of the [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine skeleton (5.98 δ, see Section 3). This anomalous value may be related to the shielding effect exerted by the phenyl ring of the pendant chiral group, and depends upon the absolute configuration of the stereogenic centre in the 3a-position, in close analogy with structurally similar pyrazolo[1,5-*a*][1,4]benzodiazepin-4-ones.[4d] Based on our previous results we were confident to assign the *R* absolute configuration to the 3a-position of diastereoisomer **10**. Some useful considerations can also be made about the hydrogen bonded to the stereogenic carbon of the chiral pendant group of **13a**, which resonates at 4.65 δ. The typical chemical shift value for such a proton encompasses the range between 6.13 and 6.38 δ,[4b] as is found for major **12a**. Careful inspection of the Dreiding stereomodels indicated that the phenyl group in the 3-position is responsible for the observed shielding effect, which is possible provided that the absolute configuration at the 3a-position is *S*. Similar statements allowed us to assign tentatively the *S* absolute configuration to the 3a-position of **13b**. These expectations were proved unambiguously by X-ray diffractometric analysis of the major isomer **12a**, which shows the *R* configuration at the newly-formed stereogenic centre at C-3a (Fig. 2 and Section 3).

As can be inferred from Table 1, the stereoselectivity of the cycloaddition varies from nil to good depending upon: (i) the dipolarophile environment and (ii) the steric bulk of the chiral auxiliary employed. Since the conjugated imino–amide moiety of **1** is essentially planar, the 1-(*S*)-phenylethyl group is forced away from the reaction site, and the incoming nitrilimine **9** can hardly discriminate between the two diastereofaces of the C=N fragment. On the other hand, the seven-membered ring of **2** can assume a boat-like conformation which enables the chiral auxiliary to hide preferentially one of the C=N diastereofaces from dipolar attack. Finally, the diastereoselectivity of the cycloaddition was scarcely influenced by the base (chiral or not).

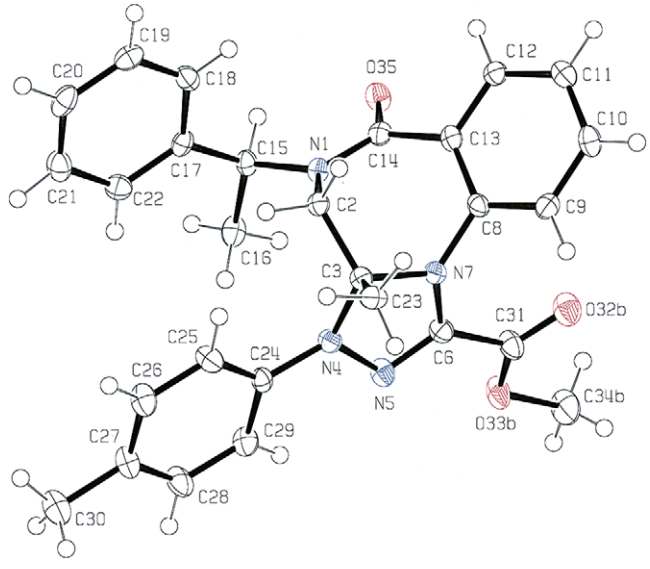


Figure 2. ORTEPIII plot of **12a** at 90 K with the crystallographic numbering scheme. The carbomethoxy group bonded to C6 is rotationally disordered around the C6–C31 bond: only the *b* conformation is reported. Ellipsoids at 50% probability level. H atoms not to scale.

3. Experimental

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. Optical rotations were recorded on a Perkin–Elmer model 241 polarimeter at the sodium D line. Compounds **3a–5a**[4b] are known in the literature.

3.1. Synthesis of *N*-[(2*S*)-3,3-dimethyl-2-butyl]-2-nitrobenzamide, 3b

A solution of (2*S*)-3,3-dimethyl-2-aminobutane (5.00 g, 0.05 mol) in dry toluene (150 mL) was added with K_2CO_3 (27.6 g, 0.20 mol). 2-Nitrobenzoyl chloride (9.25 g, 0.05 mol) in dry toluene (10 mL) was slowly added and the mixture was heated under reflux for 4 h under vigorous stirring. The undissolved material was filtered off, and the solvent was evaporated under reduced pressure. Crystallisation of the residue from hexane–benzene gave analytically pure **3b** (11.0 g, 88%); mp 153°C; $[\alpha]_D^{25}=+3.3$ (*c* 0.55, $CHCl_3$); IR (Nujol): 1640 cm^{-1}; ^{1}H NMR: δ 0.91 (9H, s), 1.13 (3H, d, $J=6.8$), 4.03 (1H, dq, $J=7.9$, 6.8), 5.50 (1H, br d, $J=7.9$), 7.4–7.6 (3H, m), 7.99 (1H, dd, $J=8.1$, 1.0); MS: *m*/*z* 250 (M^+). Anal. calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.44; H, 7.28; N, 11.24%.

3.2. Synthesis of *N*-prop-2-enyl-*N*-[(2*S*)-3,3-dimethyl-2-butyl]-2-nitrobenzamide, 4b

A solution of **3b** (4.50 g, 18.0 mmol) in dry toluene (75 mL) was treated with K_2CO_3 (3.04 g, 22.0 mmol), NaOH (2.80 g, 70.0 mmol) and $Bu_4N^+HSO_4^-$ (0.85 g, 2.5 mmol). Allyl bromide (0.85 g, 27.0 mmol) in dry toluene (7.0 mL) was added dropwise at 60°C. The mixture was warmed to 75°C for 6 h, then the undissolved material was filtered off. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum–ethyl acetate 1:3 affording **4b** as undistillable oil (3.29 g, 63% yield); $[\alpha]_D^{25}=+27$ (*c* 1.60, $CHCl_3$); IR (Nujol): 1640 cm^{-1}; ^{1}H NMR: δ 0.95 (9H, s), 1.14 (3H, d, $J=7.0$), 3.60–3.80 (2H, m), 4.90 (1H, q, $J=7.0$), 5.20–5.60 (3H, m), 7.3–7.7 (3H, m), 8.20 (1H, dd, $J=8.4$, 1.0); MS: *m*/*z* 290 (M^+). Anal. calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.21; H, 7.68; N, 9.70%.

3.3. Synthesis of *N*-prop-2-enyl-*N*-[(2*S*)-3,3-dimethyl-2-butyl]-2-amino benzamide, 5b

A solution of **4b** (2.60 g, 10.0 mmol) in ethanol (16 mL) was treated with iron powder (4.47 g, 80 mmol) and 20% aqueous acetic acid (5.0 mL), and then heated under reflux for 5 h under vigorous stirring. The mixture was extracted with ethyl acetate (100 mL) and the extract filtered through Celite. The organic layer was washed firstly with 5% aqueous sodium hydrogencarbonate (60 mL), then with water (2×50 mL), and dried over sodium sulfate. Evaporation of the solvent gave **5b** as undistillable oil (2.31 g, 89% yield); $[\alpha]_D^{25}=+56.3$ (*c* 0.78, $CHCl_3$); IR (Nujol): 3450, 3350, 3245, 1620 cm^{-1}; ^1H NMR: δ 1.00 (9H, s), 1.30 (3H, d, $J=7.3$), 4.20–4.40 (5H, m), 5.00–5.80 (3H, m), 6.6–7.1 (4H, m); MS: m/z 260 (M^+). Anal. calcd for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.77; H, 9.31; N, 9.34%.

3.4. Synthesis of 2-methyl-4-[(*S*)-1-phenylethyl]-1,4-benzodiazepin-5(3*H*)-one, 2a and 2-methyl-4-[(2*S*)-2,3,3-trimethyl-2-butyl]-1,4-benzodiazepin-5(3*H*)-one, 2b

A solution of **5a** or **5b** (8.0 mmol) in 6 M aqueous hydrochloric acid (6.0 mL) and acetic acid (3.0 mL) was treated with sodium nitrite (1.10 g, 16.0 mmol) under stirring and cooling at 0°C. After 30 min, the mixture was treated with cold diethyl ether (35 mL) and sodium azide (2.60 g, 0.04 mol) was added portionwise under vigorous stirring and ice-cooling. After 1 h, the organic layer was separated, washed with 5% aqueous sodium hydrogencarbonate (25 mL), then with water (50 mL), and dried over sodium sulfate. Evaporation of the solvent gave crude **6a** and **6b** as brown oily residues, which were used without further purification: **6a** (2.52 g, 97%), IR (neat): 2120, 1660 cm^{-1}; **6b** (2.20 g, 96%) IR (neat): 2130, 1650 cm^{-1}.

Crude **6a** or **6b** (7.8 mmol) were dissolved in toluene (30 mL) and then heated under reflux for 1 h. The solvent was evaporated and the residue was crystallised from diisopropyl ether affording pure **2a** or **2b**.

Compound 2a: 1.52 g, 70%; mp 118°C; $[\alpha]_D^{25}=-475$ (*c* 0.50, $CHCl_3$); IR (Nujol): 1635 cm^{-1}; ^1H NMR: δ 1.50 (3H, d, $J=7.2$), 1.71 (3H, s), 3.25 (1H, d, $J=14.5$), 3.34 (1H, d, $J=14.5$), 6.19 (1H, q, $J=7.2$), 7.1–7.3 (7H, m), 7.42 (1H, dd, $J=8.4$, 1.3), 8.03 (1H, dd, $J=8.4$, 8.0); MS: m/z 278 (M^+). Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.62; H, 6.55; N, 10.10%.

Compound 2b: 1.41 g, 70%; mp 178°C; $[\alpha]_D^{25}=-730$ (*c* 0.50, $CHCl_3$); IR (Nujol): 1630 cm^{-1}; ^1H NMR: δ 1.00 (9H, s), 1.30 (3H, d, $J=7.5$), 2.40 (3H, s), 3.50 (1H, d, $J=12.3$), 3.75 (1H, d, $J=12.3$), 4.90 (1H, q, $J=7.5$), 7.15–7.25 (2H, m), 7.50 (1H, dd, $J=8.3$, 8.0), 7.96 (1H, dd, $J=8.3$, 0.9); MS: m/z 258 (M^+). Anal. calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.34; H, 8.54; N, 10.76%.

3.5. General procedure for the cycloaddition between hydrazonoyl chloride 8 and enantiopure 1,4-benzodiazepinones 1 and 2

A solution of **1** (1.36 g, 6.0 mmol) and **2** (5.0 mmol) in dry dichloromethane (60 mL) was treated with base (see Table 1) under stirring at room temperature for the time indicated in Table 1. The undissolved material was filtered off, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with ethyl acetate–hexane–dichloromethane 12:4:1. First fractions contained cycloadduct **10** or major **12**, further elution gave cycloadduct **11** or minor **13** (see Table 1).

Compound 10: mp 185°C (from diisopropyl ether); $[\alpha]_D^{25}=+79$ (*c* 0.06, $CHCl_3$); IR (Nujol): 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (3H, d, $J=7.0$), 1.57 (3H, s), 2.33 (3H, s), 3.70 (1H, d, $J=14.7$), 3.75 (3H, s), 4.58 (1H, d, $J=14.7$), 5.98 (1H, dd, $J=8.1$, 1.1), 6.08 (1H, q, $J=7.0$), 6.93 (1H, dd, $J=8.1$, 7.9), 7.1–7.5 (11H, m); ^{13}C NMR ($CDCl_3$): δ 13.98 (q), 17.74 (q), 20.85 (q), 43.77 (t), 52.22 (d), 53.67 (q), 90.32 (s), 121.0–129.7, 133.68 (s), 137.36 (s), 139.51 (s), 168.56 (s), 173.77 (s); MS: m/z 468 (M^+). Anal. calcd for $C_{28}H_{28}N_4O_3$: C, 71.77; H, 6.02; N, 11.96. Found: C, 71.81; H, 6.05; N, 12.02%.

Compound 11: mp 125°C (from diisopropyl ether); $[\alpha]_D^{25}=+7$ (*c* 0.53, $CHCl_3$); IR (Nujol): 1730, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (3H, d, $J=7.2$), 1.62 (3H, s), 2.37 (3H, s), 3.68 (1H, d, $J=15.0$), 3.75 (3H, s), 4.38 (1H, d, $J=15.0$), 5.84 (1H, q, $J=7.0$), 7.0–7.4 (13H, m); ^{13}C NMR ($CDCl_3$): δ 14.16 (q), 18.21 (q), 20.68 (q), 43.60 (t), 51.91 (d), 54.16 (q), 90.13 (s), 121.0–129.0, 133.27 (s), 137.20 (s), 140.11 (s), 167.59 (s), 172.98 (s); MS: m/z 468 (M^+). Anal. calcd for $C_{28}H_{28}N_4O_3$: C, 71.77; H, 6.02; N, 11.96. Found: C, 71.74; H, 5.99; N, 12.01%.

Compound 12a: mp 195°C (from diisopropyl ether); $[\alpha]_D^{25}=-6.3$ (*c* 0.25, $CHCl_3$); IR (Nujol): 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (3H, d, $J=7.2$), 1.43 (3H, s), 2.26 (3H, s), 2.86 (1H, d, $J=16.0$), 3.47 (1H, d, $J=16.0$), 3.65 (3H, s), 6.13 (1H, q, $J=7.2$), 7.0–7.8 (13H, m); ^{13}C NMR ($CDCl_3$): δ 17.13 (q), 20.43 (q), 22.35 (q), 50.84 (t), 52.06 (d), 52.32 (q), 92.75 (s), 115.17 (s), 127.1–131.9, 134.68 (s), 136.46 (s), 139.39 (s), 140.26 (s), 169.63 (s); MS: m/z 468 (M^+). Anal. calcd for $C_{28}H_{28}N_4O_3$: C, 71.77; H, 6.02; N, 11.96. Found: C, 71.73; H, 5.96; N, 11.94%.

Compound 13a: mp 125°C (from diisopropyl ether); $[\alpha]_D^{25}=+78$ (*c* 0.45, $CHCl_3$); IR (Nujol): 1730, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.57 (3H, s), 1.75 (3H, d, $J=7.0$), 2.28 (3H, s), 3.35 (1H, d, $J=16.6$), 3.73 (3H, s), 3.80 (1H, d, $J=16.6$), 4.65 (1H, q, $J=7.0$), 6.9–7.8 (13H, m); ^{13}C NMR ($CDCl_3$): δ 17.28 (q), 20.48 (q), 22.80 (q), 50.21 (t), 51.96 (d), 52.37 (q), 92.68 (s), 115.77 (s), 127.3–131.6, 134.59 (s), 136.80 (s), 138.91 (s), 140.36 (s), 168.38 (s); MS: m/z 468 (M^+). Anal. calcd for $C_{28}H_{28}N_4O_3$: C, 71.77; H, 6.02; N, 11.96. Found: C, 71.74; H, 6.05; N, 12.02%.

Compound 12b: mp 80°C (from diisopropyl ether); $[\alpha]_D^{25} = +125.5$ (c 0.50, $CHCl_3$); IR (Nujol): 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (9H, s), 1.40 (3H, d, $J=7.2$), 1.65 (3H, s), 2.25 (3H, s), 2.54 (1H, q, $J=7.2$), 3.20 (1H, d, $J=15.8$), 3.68 (3H, s), 3.75 (1H, d, $J=15.8$), 7.0–7.7 (8 H, m); ^{13}C NMR ($CDCl_3$): δ 14.76 (q), 20.51 (q), 24.62 (q), 28.21 (q), 37.30 (s), 52.44 (q), 57.00 (t), 69.29 (d), 93.77 (s), 115.57 (s), 129.1–132.2, 130.01 (s), 134.86 (s), 138.22 (s), 139.81 (s), 140.48 (s), 158.25 (s), 168.24 (s); MS: m/z 448 (M^+). Anal. calcd for $C_{26}H_{32}N_4O_3$: C, 69.62; H, 7.19; N, 12.49. Found: C, 69.58; H, 7.23; N, 12.54%.

Compound 13b: mp 61°C (from diisopropyl ether); $[\alpha]_D^{25} = -18.6$ (c 0.25, $CHCl_3$); IR (Nujol): 1730, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.83 (9H, s), 1.44 (3H, d, $J=7.0$), 1.64 (3H, s), 2.16 (1H, q, $J=7.0$), 2.30 (3H, s), 3.15 (1H, d, $J=15.5$), 3.70 (3H, s), 3.94 (1H, d, $J=15.5$), 7.0–7.7 (8 H, m); ^{13}C NMR ($CDCl_3$): δ 14.88 (q), 20.40 (q), 23.12 (q), 30.11 (q), 37.46 (s), 52.49 (q), 55.39 (t), 69.21 (d), 91.75 (s), 115.75 (s), 129.0–132.0, 129.89 (s), 133.532 (s), 138.63 (s), 139.11 (s), 140.328 (s), 159.69 (s), 169.86 (s); MS: m/z 448 (M^+). Anal. calcd for $C_{26}H_{32}N_4O_3$: C, 69.62; H, 7.19; N, 12.49. Found: C, 69.66; H, 7.26; N, 12.54%.

3.6. Crystal data for compound 12a

$C_{28}H_{28}N_4O_3$, Fw = 468.54, orthorhombic, space group $P2_12_12_1$, $T=90$ K, $a=10.215(3)$, $b=14.519(4)$, c 16.098(4) Å, $V=2387.5(11)$ Å^3, $Z=4$, $D_{calcd}=1.304$ Mg m^{-3}, μ (Mo Kα) = 0.086 mm^{-1}; crystal dimensions 0.35×0.32×0.28 mm, $\lambda=0.71073$ Å (Mo Kα radiation, graphite monochromator, Bruker SMART-APEX CCD diffractometer, equipped with KRIO-FLEX low temperature device and software). Data collection: ω and φ scan mode, $2\theta<55.00°$; 16463 collected reflections, 3091 unique [2645 with $I_o>2\sigma(I_o)$], merging $R=0.0425$. The structure was solved by SIR-92[14] and refined by SHELXL-97[15] by full-matrix least-squares based on F_o^2, with weights $w=1/[\sigma^2(F_o)^2+(0.0522P)^2]$, where $P=(F_o^2+2F_c^2)/3$. H atoms were refined with isotropic atomic displacement parameters proportional to those of the connected atoms. The carboxymethyl group was rotationally disordered and it was modelled by two conformations with ratio 0.649:0.351; the H atoms of the disordered methyl were put in calculated position. The final consistency index were $R=0.0536$ and $R_w=0.0949$ (0.0440 and 0.0916, respectively, for observed reflections), goodness-of-fit = 0.993. The final map ranges between –0.18 and 0.27 e Å^3. The absolute configuration was determined on the base of known one at C15 (see Fig. 2). Detailed crystallographic data were deposited as CCDC 190381 with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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