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New development of Meyers' methodology: stereoselective preparation of an axially chiral 5,7-fused bicyclic lactam related to circumdatins/benzomalvins and asperlicins

Maël Penhoat, Pierre Bohn, Georges Dupas, Cyril Papamicaël, Francis Marsais and Vincent Levacher*

Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, IRCOF, CNRS, Université et INSA de Rouen, B.P. 08 F-76131 Mont-Saint-Aignan Cédex, France

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Abstract—The stereoselective preparation of a new Meyers' bicyclic lactam-bridged biaryl **1**, highly structurally related to circumdatins, benzomalvins and asperlicins, is reported. Using the popular Meyers' diastereoselective lactamization, under dehydrating conditions (CH_2Cl_2/reflux/$MgSO_4$), *trans*-(a*S*,*R*,*S*)-**1** was obtained in a rather modest yield of 25% and an excellent diastereoselectivity >95%. An alternative procedure making use of the activating agents of carboxylic acid (Mukaiyama reagent and FEP) allowed the lactamization process to take place under milder conditions (CH_2Cl_2/20 °C) affording *trans*-(a*S*,*R*,*S*)-**1** in fairly good yields (50%–85%) and in up to 65% de.

1. Introduction

The benzodiazepine moiety is found in a large number of natural products[1] and has been considered for a while as a privileged heterocyclic scaffold in lead generation for many researchers involved in CNS research programmes. The benzodiazepines constitute a well-known class of therapeutics displaying hypnotic, anxiolytic and anticonvulsant effects and still represent a widely prescribed class of psychoactive drugs.[2] In 1999, a new class of benzodiazepine alkaloids, circumdatins A–C were isolated from a terrestrial isolate of the fungus *Aspergillus ochraceus*[3] and are considered as excellent chemotaxonomic markers for this species. If any methodical screening of the biological activities of these circumdatins has been instigated, related benzomalvins A–C alkaloids, isolated from a fungus *Penicillium* sp., have already shown inhibitory activity against substance P at the guinea pig, rat and human neurokinin NK1 receptor.[4] Finally, Asperlicins, which are known as potent cholescystokinin antagonists have been isolated from the fungus *Aspergillus alliaceus*.[5] Interestingly, with regards to the stereochemistry, most of these benzodiazepine–quinazolinone alkaloids display two common configurational elements, that is, a stereogenic centre incorporated into the diazepine framework and an additional chiral axis due to restricted rotation around the C–N biaryl bond, connecting both the benzodiazepine and the quinazolone rings. This atropoisomerism is a feature of a number of natural products, which should be considered, in respect to their potential biological targets, as an important configurational element of recognition.[6] We recently extended Meyers' bicyclic lactam methodology[7] to the highly stereoselective construction of axially chiral 7,5-fused bicyclic lactams.[8] This approach presents the advantage of controlling in a single step both the stereogenic centre and the biaryl chiral axis of these axially chiral bridged biaryls. In this context, we became interested in exploring the potential of this new extension by investigating the stereoselective preparation of analogues of these benzodiazepine–quinazolinone alkaloids. Herein we report an efficient and straightforward stereoselective synthesis of analogue **1**, which may be considered as a common precursor to most of these various alkaloids (Fig. 1).

* Corresponding author. Tel.: +33 (0)2 3552 2485; fax: +33 (0)2 3552 2962; e-mail: vincent.levacher@insa-rouen.fr

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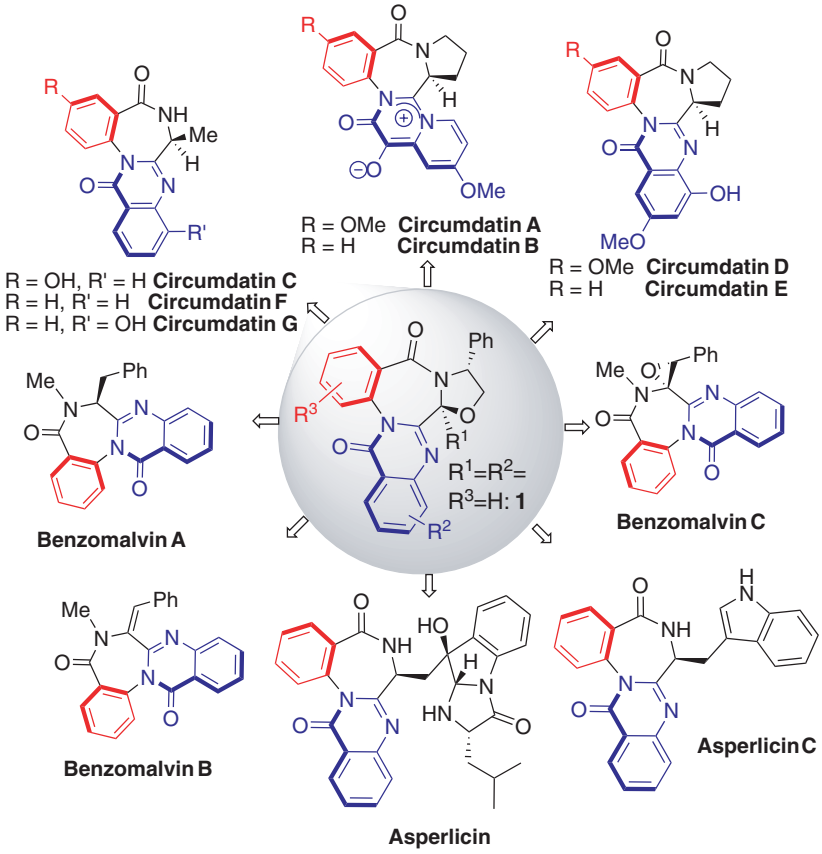
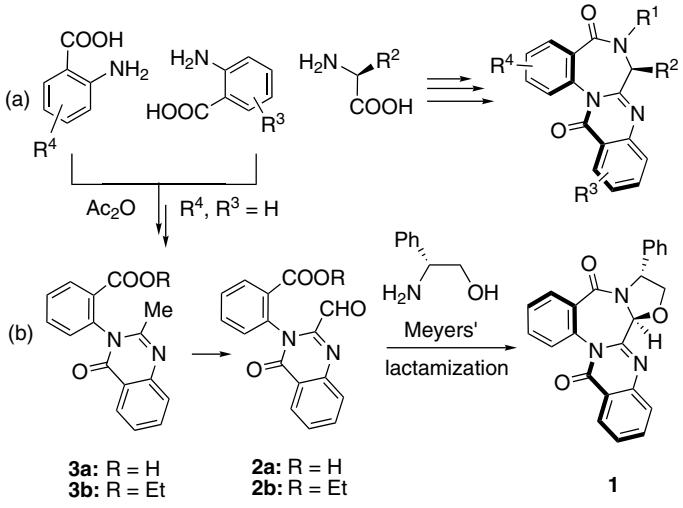


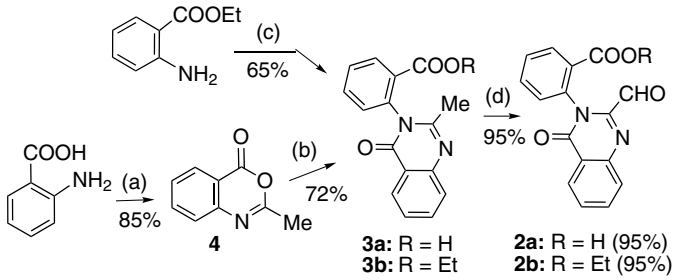
Figure 1. New axially chiral bridged biaryl benzodiazepine–quinazolinones. Potential analogues of circumdatins/benzomalvins and asperlicin.

2. Results and discussion

Most of these alkaloids have been prepared over the past 10 years.[9] A brief synthetic analysis reveals that they are formally accessible from two properly substituted anthranilic acid elements and one unit of α-amino acid (Scheme 1a). Our synthetic approach is based on a diastereoselective Meyers' lactamization of benzodiazepine–quinazolinone intermediates **2a** and **b** (Scheme 1b). Interestingly, as a result of the subordinate relationship between the absolute configuration of this chiral biaryl axis and that of the aminal centre incorporated in the benzodiazepine ring, this stereoselective ring closure is accompanied by configurational control of the chiral biaryl axis. The preparation of the key intermediates **2a** and **b** is related to those employed for the preparation of the natural alkaloids, changing the α-amino acid for acetic anhydride (Scheme 1b).



Scheme 1. (a) Previous synthetic routes to circumdatins, benzomalvins and asperlicins; (b) new stereoselective access to an analogue **1** via Meyers' lactamization of **2a**–**b**.

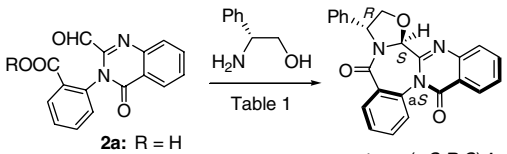


Scheme 2. Preparation of the benzodiazepine–quinazolone intermediate **2a**–**b**. Reagents and conditions: (a) Ac_2O/reflux/2 h; (b) anthranilic acid/AcOH/reflux/168 h; (c) ethyl orthoacetate (1.5 equiv)/180 °C/sealed tube/7 days; (d) SeO_2/dioxane/reflux/10 h.

Acetylanthranil **4** was prepared in 85% yield by treatment of anthranilic acid with acetic anhydride according to a literature procedure.[10] The required 2-methyl-quinazolinone **3a** was obtained in 72% yield, by treatment of **4** with a second equivalent of anthranilic acid.[11] At this stage, various attempts to convert **3a** into the corresponding ester **3b** proved to be unfruitful, leading in most cases to unidentified by-products. Alternatively, **3b** could be prepared according to a one pot procedure by reaction of ethyl *o*-aminobenzoate with ethyl orthoacetate. Ester **3b** was isolated in a fairly good yield of 65%. Finally, the desired benzodiazepine–quinazolinone intermediates **2a** and **2b** were obtained in 95% yields, in both cases, by direct oxidation of 2-methyl-quinazolinones **3a**–**b** with selenium dioxide[12] (Scheme 2).

Meyers' lactamisation of benzodiazepine–quinazolidinone **2a** and **b** was first assessed under dehydrating conditions in the presence of (*R*)-phenylglycinol at reflux in toluene solution. These classical conditions proved to be inappropriate, leading mainly to degradation of the starting materials (Table 1, entries 1 and 2). Although Meyers' methodology, has been widely exploited with various simple γ-, δ-keto acids, this failure points out the serious limitation of these classical dehydrating conditions when applied to heat-sensitive substrates. In search of milder lactamisation conditions, benzodiazepine–quinazolidinone **2a** was reacted with (*R*)-phenylglycinol in CH_2Cl_2 in the presence of $MgSO_4$ as the dehydrating agent (Table 1, entry 3). The desired lactam *trans*-(a*S*,*R*,*S*)-**1** was obtained as a single diastereoisomer (de >95%).[13] However, these new conditions still suffered from the formation of unidentified by-products furnishing lactam *trans*-(a*S*,*R*,*S*)-**1** in a rather poor yield of 25%.

Table 1. Meyers' lactamization of benzodiazepine–quinazolone intermediates **2a**–**b** under dehydrating conditions



2a: R = H
2b: R = Et

trans-(a*S*,*R*,*S*)-**1**

Entry	Substrate	Conditions	Yield (%)	de[a] (%)
1	**2a**	Toluene/reflux/24 h	0	—
2	**2b**	Toluene/reflux/24 h	0	—
3	**2a**	CH_2Cl_2/$MgSO_4$/reflux/132 h	25	>95

[a] Determined from ^1H NMR spectrum of the crude reaction mixture.

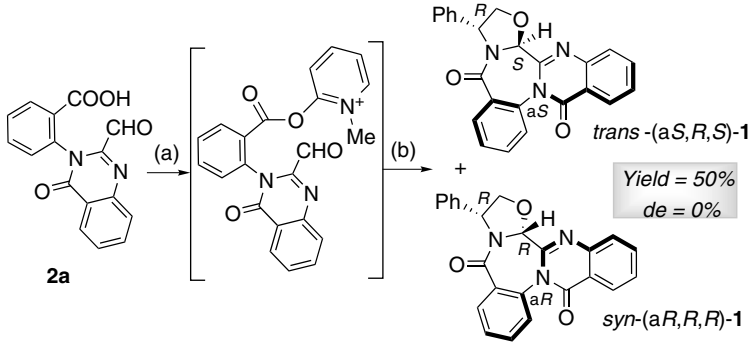
We recently developed new lactamisation conditions[14] of γ-, δ-, ω-keto acids based on the activation of carboxylic acid by means of Mukaiyama's reagent[15] (*N*-methyl-2-chloropyridinium iodide). These new activated conditions offer the advantage of accelerating the lactamisation process providing bicyclic lactams in high yields at lower temperatures. It was therefore speculated that these new activated conditions should be especially suitable for the heat-sensitive substrate **2a**. Thus, the carboxylic acid of benzodiazepine–quinazolidinone **2a** was first activated in the presence of Mukaiyama's reagent and triethylamine prior to reacting with (*R*)-phenylglycinol.

Even if these conditions could improve to some extent the conversion of **2a** into bicyclic lactam **1** (50%), a significant amount of by-products was still present in the crude. Even more disappointing was the complete absence of diatereoselectivity observed under these conditions. Both diastereoisomers *trans*-(a*S*,*R*,*S*)-**1** and *syn*-(a*R*,*R*,*R*)-**1** could be isolated by flash chromatography (Scheme 3).

Given the modest results obtained with Mukaiyama's reagent, it was next decided to employ *N*-ethyl-2-fluoropyridinium tetrafluoroborate (FEP), known to be more reactive.[16] On treating benzodiazepine–quinazolidinone **2a** with FEP in the presence of DIEA in $CHCl_3$ at 60 °C, followed by the addition of (*R*)-phenylglycinol, lactam *trans*-(a*S*,*R*,*S*)-**1** was obtained in 70% yield and a modest but still significant 20% de (Table 2, entry 1). When carrying out the same procedure in CH_2Cl_2 at 40 °C, both the yield and diastereoselectivity were notably enhanced providing lactam *trans*-(a*S*,*R*,*S*)-**1** in 80% yield and 51% de (Table 2, entry 2). The best results were finally obtained at 0 °C, affording lactam *trans*-(a*S*,*R*,*S*)-**1** in a satisfactory yield of 85% and 65% de (Table 2, entry 4). Let us note that conducting the reaction at lower temperatures (Table 2, entry 5) did not lead to any significant improvement of the diastereoselectivity.

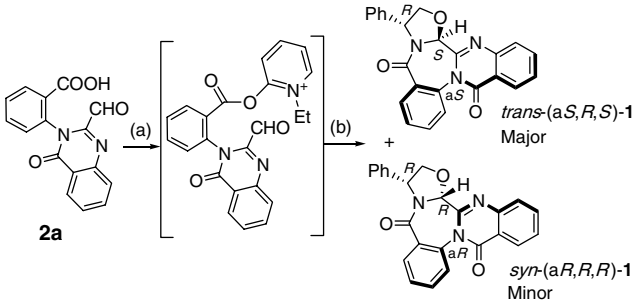
3. Conclusion

In summary, we have reported the stereoselective preparation of an axially chiral 7,5-fused bicyclic lactam **1**,



Scheme 3. Meyers' lactamization of benzodiazepine–quinazolone intermediate **2a** activated by Mukaiyama's reagent. Reagents and conditions: (a) *N*-methyl-2-chloropyridinium iodide/NEt_3/CH_2Cl_2/reflux/15 min; (b) (*R*)-phenylglycinol.

Table 2. Meyers' lactamization of the benzodiazepine–quinazolone intermediate **2a** by activation with FEP



Entry	Conditions	Yield (%)	de (%)
1	$CHCl_3$/60 °C/8 h	70	20
2	CH_2Cl_2/40 °C/8 h	80	51
3	CH_2Cl_2/20 °C/8 h	83	60
4	CH_2Cl_2/0 °C/8 h	85	65
5	CH_2Cl_2/−20 °C/8 h	83	65

Reagents and conditions: (a) FEP (*N*-ethyl-2-fluoropyridinium tetrafluoroborate)/DIEA; (b) (*R*)-phenylglycinol.

an analogue of benzodiazepine–quinazolidinone alkaloids. Attempts to apply Meyers' lactamisation to **2a** and **b** under the classical dehydrating conditions (CH_2Cl_2/reflux/$MgSO_4$) resulted in formation of the desired analogue *trans*-(a*S*,*R*,*S*)-**1** in up to 95% de, however in a poor yield of 25%. This modest yield, mainly due to the moderate stability of the starting material **2a**–**b**, reveals the limits of these reaction conditions. To circumvent this limitation, we decided to test out whether activating agents for carboxylic acids could promote the lactamisation under milder conditions. Interestingly, whereas *N*-methyl-2-chloropyridinium iodide (Mukaiyama's reagent) furnished lactam **1** in 50% yield and without diastereoselectivity, its analogue *N*-ethyl-2-fluoropyridinium tetrafluoroborate (FEP) afforded *trans*-(a*S*,*R*,*S*)-**1** in up to 65% de (85% yield). These results clearly showed the crucial role of the leaving group of the carboxylic acid on both the yield and stereoselectivity of the reaction. Further investigations to gain insight into the mechanism of bicyclic lactam formation under these new activated conditions are under way in our laboratory. Although the stereoselectivity remains medium, these new activated conditions have already demonstrated promising results in broadening the scope of Meyers' methodology to heat-sensitive substrates.

4. Experimental

4.1. General

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300. ^{1}H at 300 MHz and ^{13}C at 75 MHz using $CDCl_3$ as solvent and with the residual solvent signal (δ 7.26, ^{1}H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. The following abbreviations are used to describe peak pattern: s (singlet), d (doublet), t (triplet), q (quartet). Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 500 FT-IR spectrometer. Flash chromatographies were performed with silica 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 F_{254}).

4.2. 2-Methyl-3,1-benzoxazin-4-one 4

Compound **4** was prepared according to Ref. 10: yield = 85%. Mp 81–82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, $J = 7$ Hz, 1H), 7.48 (td, $J = 1.5$ and 7 Hz, 1H), 7.20 (m, 2H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5, 159.9, 146.7, 136.9, 128.7, 128.5, 126.7, 116.9, 21.7. IR ν_{max} (KBr): 1756, 1645, 1472, 1266, 1195, 1053, 998, 961, 779, 691 cm^{-1}. Anal. Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.01; H, 4.32; N, 8.71.

4.3. 2-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-benzoic acid 3a

To a solution of acetylanthranyl **4** (5.8 g, 36 mmol) in acetic acid (60 mL), was added anthranilic acid (5 g, 36.4 mmol). The resulting solution was refluxed for 168 h. After cooling to room temperature, the resulting precipitate was filtered and dried to afford **3a** as a white solid. Yield = 72%. Mp 256–258 °C. ^{1}H NMR (DMSO-D^6, 300 MHz) δ 13.11 (s, 1H), 8.10 (m, 2H), 7.82 (m, 2H), 7.67 (m, 2H), 7.57 (dd, $J = 0.7$ and 7.5 Hz, 1H),

7.50 (td, $J = 0.9$ and 8.3 Hz, 1H), 2.10 (s, 3H). ^{13}C NMR (DMSO-D^6, 75 MHz) δ 166.1, 161.7, 154.6, 147.8, 137.9, 134.9, 134.1, 131.95, 130.6, 129.95, 129.2, 127.0, 126.65, 126.6, 120.7, 24.1. IR ν_{max} (KBr): 1692, 1609, 1568, 1477, 1388, 1282, 1264, 1244, 1121, 779, 760, 696 cm^{-1}. MS IE (70 eV) calcd for $C_{16}H_{12}N_2O_3$: $m/z = 280$. Found: (MH^+) $m/z = 281$. Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.51; H, 4.35; N, 10.01.

4.4. 2-(2-Methyl-4-oxo-4*H*-quinazolin-3-yl)-benzoic acid ethyl ester 3b

A solution of ethyl *o*-aminobenzoate (6.18 g, 37.4 mmol) and ethyl orthoacetate ester (5.15 mL, 28.5 mmol) was refluxed for 48 h. The resultant mixture was transferred in a sealed tube and heated to 180 °C for 110 h. Trituration of the crude product with cold ethanol afforded **3b** as a yellow solid in 65% yield. When precipitation did not occur, the crude product could be purified by chromatography on silica gel (CH_2Cl_2/cyclohexane: 8/2) to afford **3b** as a yellow oil that crystallized under vacuum (72%). Mp 152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (dd, $J = 0.6$ and 6.8 Hz, 2H), 7.66 (m, 3H), 7.53 (td, $J = 0.8$ and 7.6 Hz, 2H), 7.38 (td, $J = 1.1$ and 8.3 Hz, 1H), 7.26 (dd, $J = 1.1$ and 7.9 Hz, 1H), 4.05 (q, $J = 7.1$ Hz, 2H), 2.12 (s, 3H), 0.90 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 162.8, 154.4, 148.0, 138.2, 135.0, 134.4, 133.0, 130.2, 130.0, 128.8, 127.4, 127.2, 126.9, 121.1, 61.9, 24.5, 14.0. IR ν_{max} (KBr): 1708, 1681, 1609, 1595, 1473, 1293, 1249, 787 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.21; H, 5.12; N, 9.11.

4.5. 2-(2-Formyl-4-oxo-4*H*-quinazolin-3-yl)-benzoic acid 2a

To a solution of **3a** (2.69 g, 9.6 mmol) in dioxane (50 mL), was added freshly prepared SeO_2 (1.06 g, 9.6 mmol), then the resulting mixture refluxed for 3 h. The cooled solution was filtered through a plug of celite 545. The plug of celite was washed with dioxane (2×15 mL) and the solvent was evaporated to afford **2a** in 95% yield as a yellow oil. Recrystallization in toluene provided **2a** as a yellow solid. Mp 80 °C (dec). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.44 (s, 1H), 8.83 (s, 1H), 8.22 (d, $J = 7.6$ Hz, 1H), 8.06 (d, $J = 6.9$ Hz, 1H), 7.78 (m, 2H), 7.64–7.46 (m, 4H), 7.17 (d, $J = 6.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.2, 168.0, 162.1, 147.25, 146.6, 137.0, 135.2, 134.4, 132.8, 130.2, 129.0, 127.8, 127.3, 122.8, 121.6. IR ν_{max} (KBr): 1724, 1693, 1601, 1288, 1236, 774, 695. HRMS IE (70 eV) calcd for $C_{16}H_{10}N_2O_4$: 294.0640; found: 294.0638.

4.6. 2-(2-Formyl-4-oxo-4*H*-quinazolin-3-yl)-benzoic acid ethyl ester 2b

Compound **2b** was prepared from compound **3b** according to the procedure reported above. Yield = 95%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.51 (s, 1H), 8.27 (d, $J = 7.5$ Hz, 1H), 8.14 (d, $J = 7.5$ Hz, 1H), 7.90–7.78 (m, 2H), 7.67–7.51 (m, 3H), 7.22 (d, $J = 7.0$ Hz, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 0.99 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.4, 165.1, 162.0, 147.4, 146.9, 136.8, 135.4, 133.9, 132.4, 130.3, 130.2, 129.8, 129.2, 128.0, 127.9, 122.9, 61.7, 14.2. IR ν_{max} (KBr): 1720, 1691, 1608, 1293, 1266, 1114, 775, 698. HRMS IE (70 eV) calcd for $C_{18}H_{14}N_2O_4$: 322.0953; found: 322.0945.

4.7. Meyers' lactamization by activation with FEP (typical procedure)

To a solution of **2a** (2.52 g, 8.6 mmol) in CH_2Cl_2 (50 mL) was added DIEA (2.22 g, 17.2 mmol) and FEP (1.83 g, 9.4 mmol). The resultant solution was stirred at room temperature for 15 min, after which (*R*)-phenylglycinol (1.18 g, 8.6 mmol) was added. The solution was stirred for a further 8 h, filtered and the solvent evaporated under vacuum. The diastereoselectivity (de = 60% in favour of *trans*-(a*S*,*R*,*S*)-**1**) was determined from the ^{1}H NMR of the crude reaction mixture. The residue was purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 8/2) affording both diastereoisomers *trans*-(a*S*,*R*,*S*)-**1** in 70% yield ($R_f = 0.52$) and *syn*-(a*R*,*R*,*R*)-**1** in 13% yield ($R_f = 0.35$). Selected data for *trans*-(a*S*,*R*,*S*)-**1**: mp > 250 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, $J = 7.9$ Hz, 1H), 7.77 (m, 3H), 7.58–7.43 (m, 4H), 7.33–7.23 (m, 5H), 5.98 (s, 1H), 5.21 (d, $J = 6.4$ Hz, 1H), 5.02 (dd, $J = 6.8$ and 9.6 Hz, 1H), 4.31 (d, $J = 9.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.8, 161.5, 151.5, 146.4, 140.3, 135.6, 132.7, 131.7, 130.3, 129.7, 129.3 (2×), 129.2, 128.5, 128.45, 128.4, 128.0, 126.65 (2×), 122.0, 85.0, 76.1, 59.3. IR ν_{max} (KBr): cm^{-1}. $[\alpha]_D^{20} = -93.2$ (*c* 3.4, CH_2Cl_2). HRMS IE (70 eV) calcd for $C_{24}H_{17}N_3O_3$: 395.1270; found: 395.1265. Selected data for *syn*-(a*R*,*R*,*R*)-**1**: mp 204 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, $J = 7.9$ Hz, 1H), 7.97 (dd, $J = 1.1$ and 8.3 Hz, 1H), 7.83–7.60 (m, 2H), 7.58–7.45 (m, 4H), 7.12–7.08 (m, 5H), 5.86 (s, 1H), 5.19 (t, $J = 7.5$ Hz, 1H), 4.68 (dd, $J = 7.5$ and 9 Hz, 1H), 4.58 (t, $J = 7.5$ and 9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 160.3, 150.9, 144.8, 135.9, 134.3, 131.4, 130.8, 130.3, 129.4 (2×), 128.2, 128.0, 127.8, 127.1, 127.1, 127.0, 126.7, 125.7 (2×), 120.5, 84.1, 74.95, 59.4. $[\alpha]_D^{20} = +130.9$ (*c* 7.15, CH_2Cl_2). HRMS IE (70 eV) calcd for $C_{24}H_{17}N_3O_3$: 395.1270; found: 395.1274.

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