

# Solid-Support Synthesis of Natural Product-like Compounds Derived from D-(–)-Ribose

Roland Messer,<sup>a</sup> Xavier Pelle,<sup>b</sup> Andreas L. Marzinzik,<sup>b</sup> Hansjörg Lehmann,<sup>b</sup> Jürg Zimmermann,<sup>b</sup> Robert Häner<sup>\*a</sup>

<sup>a</sup> Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland  
Fax +41(31)6318057; E-mail: robert.haener@ioc.unibe.ch

<sup>b</sup> Novartis Institutes of BioMedical Research, 4002 Basel, Switzerland

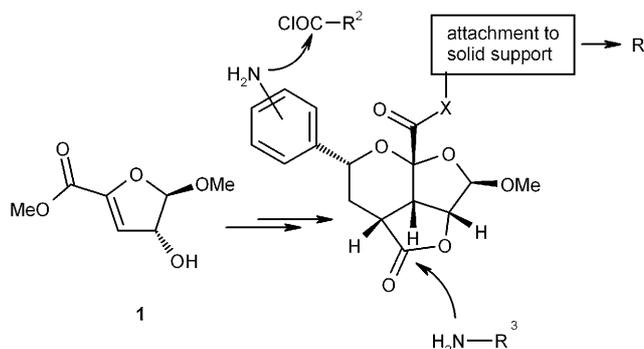
Received 3 August 2005

**Abstract:** The synthesis of natural product-like compounds on solid support is described. Starting from a readily accessible D-(–)-ribose derivative, a tricyclic scaffold is prepared in five steps. After coupling onto solid supports bearing different substituents (PAL resins), the scaffold can be further derivatised at two diversity points. Representative derivatives obtained by this diversity-oriented procedure are described.

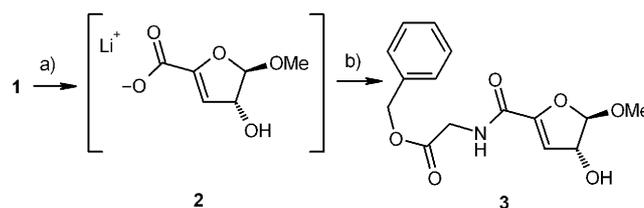
**Key words:** solid-phase synthesis, hetero Diels–Alder reactions, medicinal chemistry, combinatorial, furans

Many existing drugs are either natural products or are derived from naturally occurring compounds.<sup>1</sup> It is, thus, not surprising that a considerable effort in the search for new lead compounds is devoted to the synthesis of natural product-like libraries.<sup>2</sup> Tricyclic iridoid-derived structures, such as euplotin and udoteatrial, represent an interesting class of compounds with a variety of biological activities.<sup>3</sup> Therefore, they serve as a guiding motif for the synthesis of natural product-like compounds. We have recently described the synthesis of a tricyclic scaffold starting from D-(–)-ribose.<sup>4</sup> The key step of the synthesis involves a highly selective intramolecular hetero Diels–Alder reaction leading to a single diastereomeric product. We also showed that the scaffold was amenable to further derivatisation in solution-phase. For the preparation of larger compound libraries, however, the synthesis on solid-phase has practical advantages.<sup>5</sup> In this letter we wish to report the elaboration of a solid-phase synthesis enabling the generation of multi-dimensional compound libraries, as illustrated in Scheme 1.

Starting point of the synthesis was the unsaturated furanose **1**, which is easily accessible from D-(–)-ribose.<sup>6</sup> Direct attachment to a solid support through the carboxylic acid function of **1** was, however, not advised since steric hindrance in the later tricyclic derivatives was likely to lead to problems. To avoid these difficulties, an additional glycine linker was introduced early in the synthesis (Scheme 2). Thus, compound **1** was treated with one equivalent of lithium hydroxide in a mixture of dioxane and water (5:1) to give the lithium carboxylate **2**, which



**Scheme 1** Preparation and derivatisation of a solid-support-bound tricyclic intermediate synthesised from a D-(–)-ribose derivative



**Scheme 2** Preparation of the unsaturated furanose **3**. *Reagents and conditions:* a) 0.5 N LiOH, dioxane–H<sub>2</sub>O (5:1), quant.; b) glycine benzylester, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), *N,N*-diisopropylethylamine, MeCN, r.t., 4 h, 97%

was directly converted into the amide **3** in 97% overall yield.

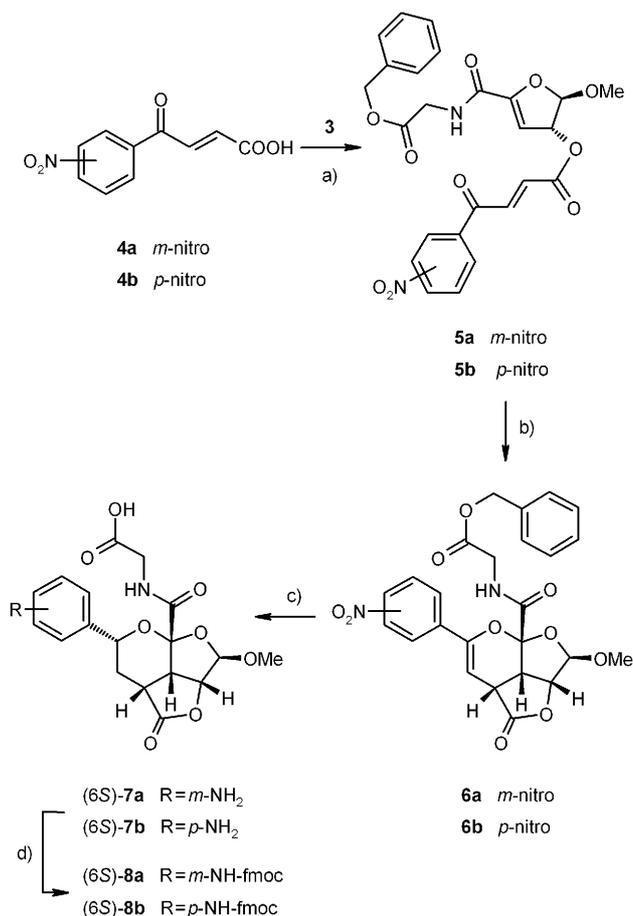
Next, the oxadiene moiety required for the hetero Diels–Alder reaction was introduced. The nitro-derived benzoyl acrylic acids **4** were chosen for this purpose. Both, the *meta*- and the *para*-isomers were prepared as described in the literature.<sup>7</sup> Esterification involved formation of the mixed anhydride of the acids **4** with pivaloyl chloride, which were further reacted with **3** in the presence of *N,N*-dimethyl-4-aminopyridine (Scheme 3). The moderate yields of the esters **5a** and **5b** obtained with both acids (45% in each case) are mostly due to the lability of the acrylic acids under the conditions required for esterification.<sup>8</sup>

Esters **5a** and **5b** underwent cyclisation in toluene at 100 °C within 24 hours to give the corresponding products **6a** and **6b** in yields of approximately 45%.<sup>9</sup> In both

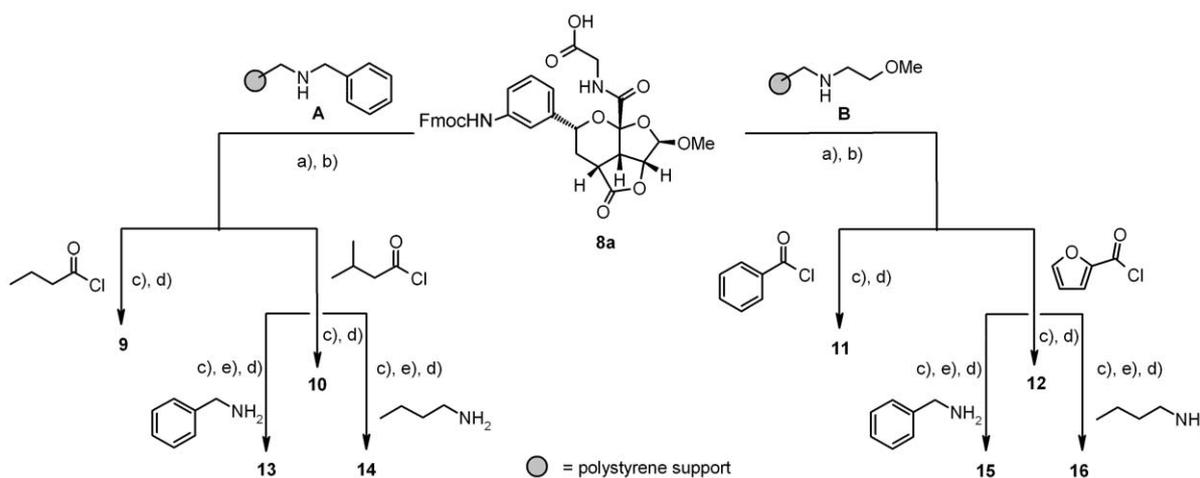
cases, the intramolecular hetero Diels–Alder reaction gave a single product, which is in agreement with the high stereoselectivity observed with a similar derivative.<sup>4</sup> Hydrogenation of the scaffolds **6a** and **6b** involved cleavage of the benzyl ester, reduction of the nitro group as well as of the enol ether. Again, compounds **7a** and **7b** were obtained as single diastereomers. The hydrogenation was carried out in THF due to slow *trans*-esterification if methanol was used as solvent. Without further purification, the anilines **7a** and **7b** were protected with Fmoc-Cl to give products **8a** and **8b** after crystallisation from methyl *tert*-butyl ether and methanol in yields of 78% based on **6a** and 52% based on **6b**, respectively.

For the synthesis of combinatorial compound libraries we decided to use N-substituted PAL resins.<sup>10</sup> The N-substituted PAL resin features the advantage of derivatising the carboxylic acid moiety in the coupling step by secondary amide formation, thus providing a third possibility of introducing diversity. Two examples of solid-support-mediated libraries were made from the Fmoc-protected scaffold **8a**. In these model libraries, the two N-substituted PAL resins **A** and **B** (Scheme 4) were used containing a benzyl amine and a 2-methoxy ethylamine residue, respectively. The immobilisation of **8a** worked best using a combination of HCTU<sup>11</sup> and 1-hydroxybenzotriazole (HOBT) in *N*-methyl pyrrolidone (NMP). The immobilized aniline **8a** was deprotected with 20% piperidine in *N,N*-dimethyl acetamide (DMA). Quantification by UV spectrometry indicated a loading of approximately 60%.<sup>12</sup>

Each batch of the functionalised solid supports **A** and **B** was split into two unequal portions of 1/4 and 3/4. Acylation was then performed as shown in Scheme 4 using different acyl chlorides in pyridine–dichloromethane. The smaller portions were cleaved from the support directly after acylation, leading to the products **9** and **11**. The larger portions were split again into three equal portions. One portion of each kind (**A** and **B**) was

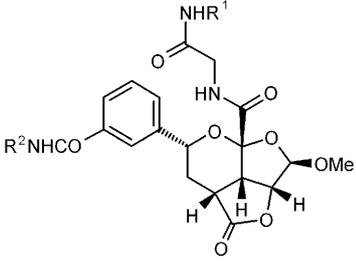
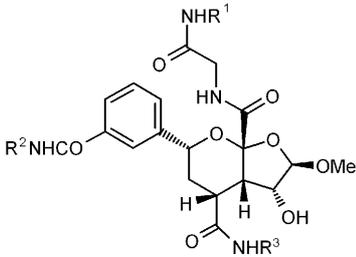


**Scheme 3** Synthesis of the Fmoc-protected aniline acid scaffolds **8a** and **8b**. *Reagents and conditions*: a) pivaloyl chloride, Et<sub>3</sub>N, *N,N*-dimethyl-4-aminopyridine, 1,2-dichloroethane, 0 °C, 2 h, 45% (for **5a** and **5b**); b) toluene, 100 °C, 24 h (**6a**: 45%; **6b**: 44%); c) Pd/C (10%), H<sub>2</sub>, THF; d) Fmoc-Cl, NaHCO<sub>3</sub>, dioxane–H<sub>2</sub>O (**8a**: 78%; **8b**: 52% over two steps)



**Scheme 4** Schematic illustration of combinatorial synthesis of compounds **9–16**. Intermediate **8a** was linked to PAL resins **A** and **B** containing a benzyl and a 2-methoxy aminoethyl moiety, respectively. *Reagents and conditions*: a) HCTU–1-hydroxybenzotriazole, *N,N*-diisopropylethylamine (DIPEA), *N*-methyl pyrrolidone; b) piperidine–*N,N*-dimethylacetamide (1:4); c) pyridine–CH<sub>2</sub>Cl<sub>2</sub> 1:4; d) H<sub>2</sub>O–TFA–CH<sub>2</sub>Cl<sub>2</sub> (1:19:80); e) 2-hydroxy pyridine (5 equiv), THF

**Table 1** Products Synthesized through Derivatisation of the Solid-Support-Bound Intermediate **8a**

Product	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%) <sup>a</sup>	
	<b>9</b>	Benzyl	Butyl	–	55
	<b>10</b>	Benzyl	Isobutyryl	–	54
	<b>11</b>	2-Methoxyethyl	Benzoyl	–	59
	<b>12</b>	2-Methoxyethyl	2-Furanyl	–	71
	<b>13</b>	Benzyl	Isobutyryl	Benzyl	46
	<b>14</b>	Benzyl	Isobutyryl	Butyl	39
	<b>15</b>	2-Methoxyethyl	2-Furanyl	Benzyl	70
	<b>16</b>	2-Methoxyethyl	2-Furanyl	Butyl	63

<sup>a</sup> Overall yields [steps c)–e), see Scheme 4] isolated after HPLC purification.

cleaved from the support to give the products **10** and **12**. The remaining two portions of each support were further submitted to aminolysis of the lactone leading to the products **13–16**. The structures of the eight products obtained in this way are shown in Table 1. Aminolysis of the lactone was best achieved by the use of 2-hydroxy pyridine.<sup>13</sup> Simple treatment with an amine in the absence of the catalyst did not lead to formation of the desired amides. Cleavage from the solid support was carried out using a mixture of aqueous trifluoroacetic acid in dichloromethane.

The crude products were finally purified using normal phase HPLC to obtain the individual compounds shown in Table 1.

It is important to note here that no signs of decomposition were observed under the acidic conditions required for release of the products from the solid support. Since the obtained, highly functionalised polycyclic compounds are based on acetal-type structures, this might well be expected. The hydrolytic stability of the scaffolds is, furthermore, an important aspect for potential medicinal applications. Both acetal groups present in the scaffold were, however, completely resistant to treatment with aqueous trifluoroacetic acid at room temperature for one day.

In conclusion, a polycyclic scaffold with high structural similarity to several natural products has been elaborated to meet the requirements of solid-phase synthesis. The scaffold was constructed from a D-(–)-ribose-derived intermediate through an intramolecular hetero Diels–Alder reaction. The obtained tricyclic derivative was further transformed by straightforward chemical reactions into a substrate suitable for immobilisation on N-substituted

PAL resins. The immobilised scaffold, bearing six stereocentres, was shown to be amenable to derivatisation in a diversity-oriented manner. Two small exemplary libraries were prepared to demonstrate the usefulness of this approach.

#### General Procedure

##### Functionalisation of the PAL-Resins

Resin **A** or **B** (150 mg) containing 0.6–0.7 mmol of available amino groups per gram were placed into a syringe containing a filter. The resin was suspended in NMP (3 mL), agitated well and allowed to swell for 30 min. After displacement of the solvent, a solution of **8a** (148 mg, 240 μmol), HCTU (100 mg, 240 μmol) and HOBT (33 mg, 240 μmol) in NMP (2 mL) was added to the resin followed by DIPEA (148 μL, 880 μmol). The suspension was gently agitated over night. The solution was displaced and the resin was treated with the same reagents [HCTU (68 mg, 165 μmol) together with HOBT (22 mg, 165 μmol) and **8a** (101 mg, 165 μmol) dissolved in 2 mL NMP followed by DIPEA (148 μL, 880 μmol)] a second time (5 h). The resin was washed successively with degassed DMA (5 × 1 mL), *i*-PrOH (1 mL), DMA (3 × 1 mL), *i*-PrOH (5 × 1 mL), CH<sub>2</sub>Cl<sub>2</sub> (2 × 1 mL) and degassed DMA (2 × 1 mL). The resin was flushed continuously with 30 mL of a 20% solution of piperidine in DMA over a period of 30 min. The eluent was collected and diluted with MeOH to 100 mL for UV spectrophotometric quantification of the loading.<sup>12</sup>

##### Derivatisation of the Functionalised Supports by Acylation

The resin derivatised with **8a** was washed by repeating the procedure described in the previous step followed by an additional final washing step with CH<sub>2</sub>Cl<sub>2</sub>. The resin was suspended in a minimally required amount of CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and split into 2 portions of 1/4 and 3/4. Each portion was treated separately with an excess of the corresponding acyl chloride (20 equiv, see Scheme 4) in CH<sub>2</sub>Cl<sub>2</sub>–pyridine (8:2, 0.4 or 1.2 mL, respectively). The suspensions were gently agitated for 3 h. The resins were again washed in the typical

procedure including an additional final washing step with  $\text{CH}_2\text{Cl}_2$  (1 mL). The portions carrying compounds **9** and **11** were put aside for the final cleaving step. The remaining two portions were again suspended in  $\text{CH}_2\text{Cl}_2$  (1.5 mL). The material was split into 3 equal fractions. One fraction of each series (containing compounds **10** and **12**) was again saved for final cleavage from the support. The two remaining portions of each series were further derivatised as described below.

#### Aminolysis of the Lactone

The remaining portions of resin obtained as described above were treated with an excess of the corresponding amine (20 equiv) in the presence of 2-hydroxy pyridine (4 equiv) in 0.5 mL THF.

#### Cleavage of the Products from the Supports

The compounds so obtained were cleaved from the support by five repetitive treatments with 0.6 mL of a mixture of  $\text{H}_2\text{O}$ –TFA– $\text{CH}_2\text{Cl}_2$  (1:19:80) for 15 min. The thus obtained solutions containing the products were collected in round-bottom flasks and concentrated. The obtained crude materials (purity generally >80%) were re-dissolved in MeOH and concentrated again before purification by normal phase HPLC (LiChrospher® Si 60, 10  $\mu\text{m}$ ) using isocratic elution with MeCN.

#### (2R,2aR,4aS,6S,7aS,7bS)-6-{3-[(Furan-2-carbonyl)amino]phenyl}-2-methoxy-4-oxohexahydro-1,3,7-trioxacyclopenta[cd]indene-7a-carboxylic Acid [(2-Methoxyethyl-carbamoyl)methyl]amide (**12**)

Yield 6.0 mg (71%). TLC (MeCN):  $R_f = 0.46$ ; HPLC:  $t_R = 8.55$ ,  $\lambda_{\text{max}} = 276$  nm.  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ ):  $\delta = 9.46$  (1 H, br), 7.94–7.90 (1 H, t), 7.76–7.75 (1 H, m), 7.69 (1 H, m), 7.73 (1 H, br), 7.37–7.31 (1 H, t,  $J = 7.9$  Hz), 7.24–7.23 (1 H, m), 7.19–7.16 (1 H, m), 7.10 (1 H, br), 6.66–6.64 (1 H, m), 5.28 (1 H, s), 4.93 (1 H, d,  $J = 6.2$  Hz), 4.81 (1 H, dd,  $J = 9.7, 6.5$  Hz), 4.01–3.86 (3 H, m), 3.42 (3 H, s), 3.42–3.34 (5 H, m), 3.24 (3 H, s), 2.44–2.19 (2 H, m).  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ ):  $\delta = 178.1, 169.6, 169.2, 157.1, 146.0, 143.4, 139.8, 129.7, 122.7, 120.5, 120.4, 119.2, 115.4, 113.0, 107.7, 84.9, 73.4, 71.8, 58.7, 55.9, 43.3, 39.8, 39.0, 36.4, 28.3$ . ESI-MS (positive mode): 566 [ $\text{M}^+ + \text{Na}^+$ ], 544 [ $\text{M}^+$ ], 512. HRMS:  $m/z$  calcd for  $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_{10}\text{Na}$ : 566.1750; found: 566.1769.

#### (2R,3R,3aS,4S,6S,7aS)-6-{3-[(Furan-2-carbonyl)amino]phenyl}-3-hydroxy-2-methoxyhexahydrofuro[2,3-b]pyran-4,7a-dicarboxylic Acid 4-Benzylamide 7a-[(2-methoxyethyl-carbamoyl)methyl]amide (**15**)

Yield 7.0 mg (70%). TLC (EtOAc):  $R_f = 0.15$ ; HPLC:  $t_R = 8.61$ ,  $\lambda_{\text{max}} = 277$  nm.  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ ):  $\delta = 9.47$  (1 H, br), 8.26 (1 H, br), 7.92–7.88 (1 H, m), 7.77 (1 H, m), 7.75–7.74 (1 H, m), 7.73–7.72 (1 H, m), 7.37–7.18 (9 H, m), 6.65–6.63 (1 H, m), 5.13 (1 H, s), 4.92 (1 H, dd,  $J = 11.9, 2.3$  Hz), 4.49 (2 H, s), 4.28 (1 H, d,  $J = 6.0$  Hz), 3.98–3.82 (2 H, m), 3.38–3.36 (5 H, m), 3.36 (3 H, s), 3.24 (3 H, s), 2.93–2.89 (2 H, m), 2.43–2.31 (1 H, m), 1.88–1.82 (1 H, m).  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ ):  $\delta = 175.0, 169.8,$

169.2, 157.0, 149.3, 146.0, 143.8, 140.1, 139.6, 129.5, 129.4, 129.1, 128.4, 129.1, 127.9, 123.0, 120.3, 119.0, 115.3, 113.0, 112.2, 106.4, 78.5, 76.0, 71.8, 58.7, 55.7, 43.8, 42.8, 42.0, 41.4, 39.7, 34.3. ESI-MS (positive mode): 674 [ $\text{M}^+ + \text{Na}^+$ ], 651 [ $\text{M}^+$ ], 621, 620. HRMS:  $m/z$  calcd for  $\text{C}_{33}\text{H}_{38}\text{N}_4\text{O}_{10}\text{Na}$ : 637.2485; found: 673.2480.

#### Acknowledgment

Financial support by the Swiss National Foundation (grant 200021-101861/1) is gratefully acknowledged. We thank L. Moesch for excellent technical assistance.

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- (12) The loading efficiency was determined by UV spectrometric quantification of the dibenzofulvene–piperidine adduct formed during deprotection ( $\lambda_{\text{max}} = 302$  nm,  $\epsilon = 7800$ ), see: Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, 3404.
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