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Efficient Solid-Phase Synthesis of Symmetric Norbinaltorphimine Derivatives

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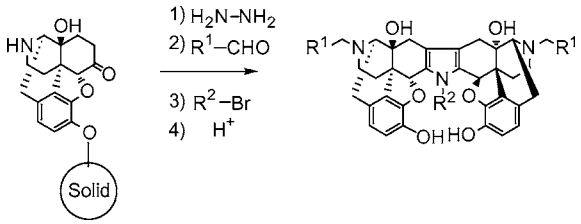
ABSTRACT



We describe an efficient solid-phase synthesis of symmetric norbinaltorphimine (norBNI) derivatives 2. Pyrrole formation involving the homocoupling of two solid-supported ketones 6, followed by chemoselective and sequential N-alkylation, provided N-substituted norBNI derivatives 2. Use of this methodology led to the combinatorial synthesis of 120 norBNI derivatives.

Chemical genomics is providing new and attractive methodologies for the discovery of new drug targets using biologically active small molecules.[1] Dimeric molecules are effective templates that show unique biological activity.[2] Therefore, effective methods for the synthesis of the dimeric molecules are required.

Solid-phase synthesis is a powerful method for the synthesis of combinatorial libraries because of the ease of workup and purification and applicability to a split-pool strategy.[3,4] Coupling reactions of solid-supported substrates are effective for the synthesis of symmetrical dimeric molecules. Schreiber et al. have recently reported a coupling reaction of solid-supported oligopeptides along with alkene side-chain by olefin metathesis.[5] We envisaged that substrates highly loaded on a resin would allow for interchain reactions on a solid phase, providing complex skeletons. The methodology would be effective for the synthesis of combinatorial libraries composed of the symmetric skeletons.

Norbinaltorphimine (norBNI (**1**)) composed of a symmetric pyrrole skeleton is a highly selective κ-opioid antagonist[6] (Scheme 1). Selective agonists and antagonists of the opioid receptors are important not only for drug

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(2) Clemons, P. A. *Curr. Opin. Chem. Biol.* **1999**, *3*, 112−115.

(3) In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; Vols. 1 and 2.

(4) For our reported solid-phase synthesis of a small-molecule library, see: (a) Matsuda, A.; Doi, T.; Tanaka, H.; Takahashi, T. *Synlett* **2001**, 1101−1104. (b) Hijikuro, I.; Doi, T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716−3722. (c) Ohno, H.; Kawamura, K.; Ohtake, A.; Nagase, H.; Tanaka, H.; Takahashi, T. *Synlett* **2002**, 93−96. (d) Fuchi, N.; Doi, T.; Cao, B.; Kahn, M.; Takahashi, T. *Synlett* **2002**, 285−289. (e) Tanaka, H.; Zenkoh, T.; Setoi, H.; Takahashi, T. *Synlett* **2002**, 1427−1430. (f) Tanaka, H.; Ohno, H.; Kawamura, K.; Ohtake, A.; Nagase, H.; Takahashi, T. *Org. Lett.* **2003**, *5*, 3053−3057.

(5) For an example of intraside dimerization reaction of solid-supported substrates, see: (a) Blackwell, H. E.; Clemons, P. A.; Schreiber, S. L. *Org. Lett.* **2001**, *3*, 1185−1188. (b) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909−912. (c) Liao, Y.; Fathi, R.; Yang, Z. *J. Comb. Chem.* **2003**, *5*, 79−81.

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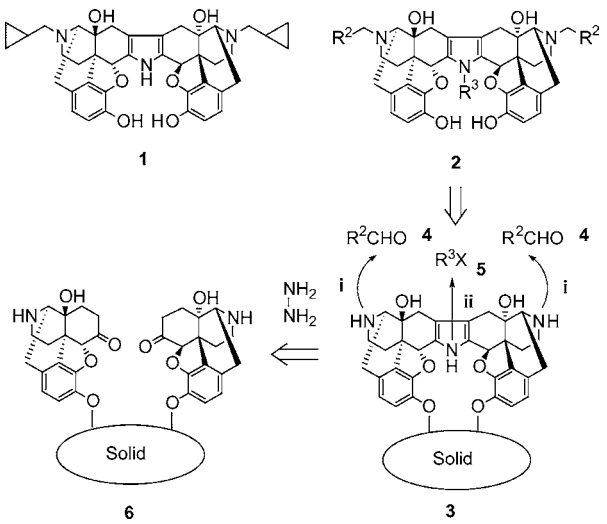
Scheme 1. Strategy for the Solid-Phase Synthesis of NorBNI Derivatives **2**

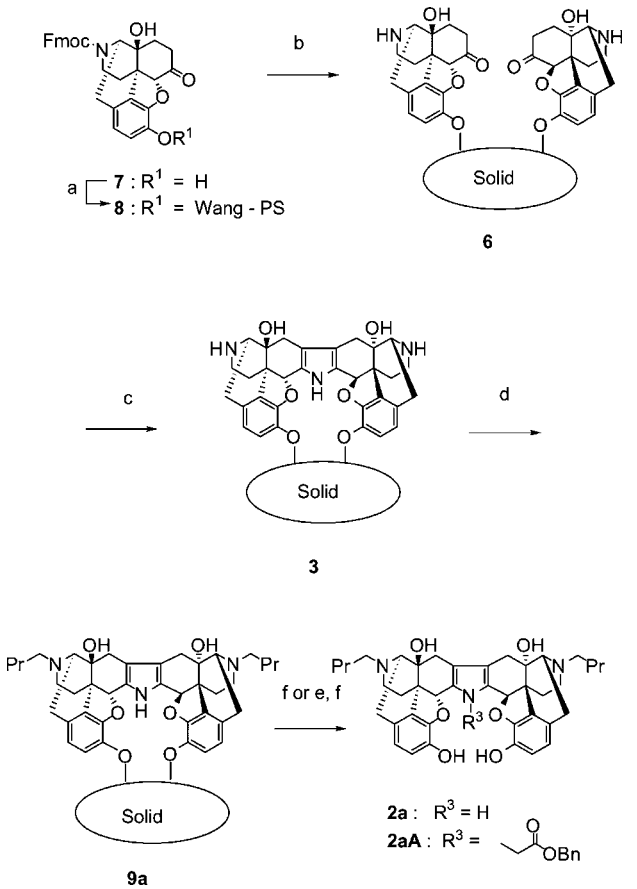


discovery but also biological evaluation. On the basis of the "message−address concept",[7] free phenols and *tert*-amines have been shown to be the important functional groups required for their biological activity. Additionally, substituents at the *N*-17 and 17′ positions are essential for selective binding to the receptor. Synthesis of norBNI derivatives **2** has been achieved using Piloty synthesis[8] of naltrexone.[9] However, their high polarity derived from the phenols and the amines requires laborious purification. Therefore, effective and practical methods for the synthesis of the norBNI derivatives **2** are required. Herein, we describe an efficient solid-phase synthesis of symmetric tri-N-substituted norBNI derivatives **2** by coupling reaction of two solid-supported ketones.

Our strategy for the solid-phase synthesis of norBNI derivatives **2** is shown in Scheme 1. A solid-supported pyrrole **3** is a key intermediate for the solid-phase synthesis of **2**. Chemoselective and sequential N-alkylations (**i** and **ii)** of amines at the *N*-17 and 17′ positions of **3** with two aldehydes **4** and the pyrrolic nitrogen with alkyl halide **5**, followed by cleavage, would provide tri-N-substituted norBNI derivatives **2**. Preparation of **3** would be achieved by Piloty synthesis of solid-supported ketones **6**. Complete loading of **6** would be effective for the interchain reaction. Although complete functionalization of the resin requires excess **7**, the excess can be recovered for reuse after a simple purification.

We first conducted the solid-phase synthesis of the *N*,*N*′-di-butyl derivative **2aA**. Exposure of Wang resin to a solution of **7**[4f] in the presence of diethylazodicarboxylate (DEAD) and PPh_3 provided solid-supported ketone **8**. The loading yield of **8** was estimated by measurement of the weight of the cleaved material **7** and found to be 99% yield based on the resin. Removal of the Fmoc group with piperidine provided amine **6**. Ketone **6** was treated with hydrazine dihydrochloride in DMF at 50 °C for 16 h. Piloty synthesis smoothly proceeded under these reaction conditions to provide di-sec-amine **3**.[10] Selective N-alkylation of diamine **3** at the 17 and 17′ positions was achieved by treatment with butyl aldehyde (**4a**) and $NaCNBH_3$ to afford dibutylamine **9a** in 65% yield with 76% purity, which was determined by HPLC analysis of the cleaved material **2a** using UV absorption at 254 nm. It should be noted that uncoupled ketone derivatives were not detected in the crude mixture by mass spectra. N-Alkylation of pyrrole **9a** with benzyl α-bromoacetate (**5a**) in the presence of *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP), followed by cleavage under acidic conditions provided norBNI derivatives **2aA** in 56% yield with 74% purity, which was estimated by HPLC analysis on the basis of UV absorption at 254 nm.[11] Further purification of **2aA** was achieved by reverse-phase HPLC to provide **2aA** in 14% isolated yield in five steps based on **8**. We next planned the combinatorial synthesis of norBNI

Scheme 2[a]



[a] Reagents and conditions: (a) Wang resin, PPh_3, DIEA, THF, rt, 16 h; (b) piperidine, DMF, rt,16 h; (c) hydrazine dihydrochloride, DMF, 50 °C, 24 h; (d) **4a**, 1% AcOH/DMF, rt, 1 h, then sodium cyanoborohydride, rt, 16 h; (e) BTPP, rt, 1 h, then **5A**, DMF, rt, 16 h; (f) 10%TFA, CH_2Cl_2, rt, 1 h.

(7) (a) Portoghese P. S.; Lipkowski A. W.; Takemori A. E. *J. Med. Chem.* **1987**, *30*, 238−239. (b) Portoghese P. S.; Sultana M.; Nagase H.; Takemori A. E. *J. Med. Chem.* **1988**, *31*, 281−282.

(8) (a) Piloty, O. *Ber*. **1910**, *43*, 489−498. (b) Robinson, G. M.; Robinson, R. *J. Chem. Soc.* **1918**, *113*, 639−645. (c) Posvic, H.; Dombro, R.; Ito, H.; Telinski, T. *J. Org. Chem.* **1974**, *39*, 2575−2580.

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derivatives **2** containing 10 N-free pyrroles **2a**−**j** and 110 N-alkylated pyrroles **2aA**−**jK**. Ten aldehydes **4a**−**j** and 11 halides **5A**−**K** were used as building blocks (Figure 1). The

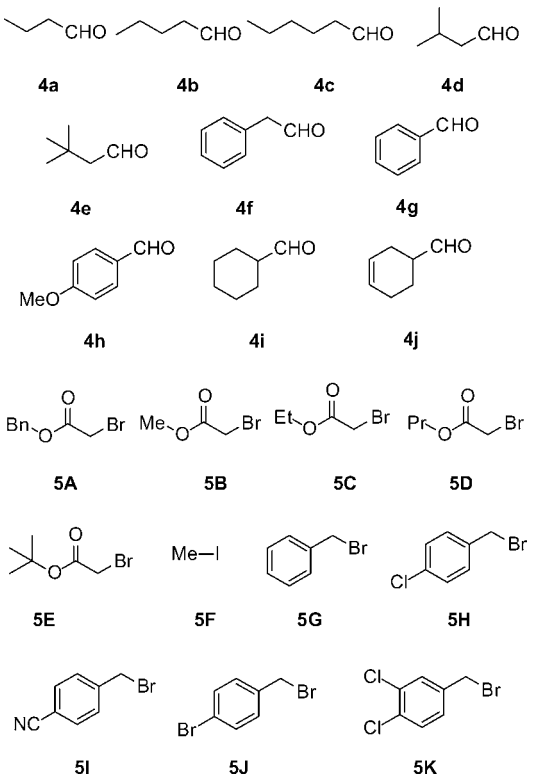

Figure 1. Building blocks **4** and **5** for the library synthesis of norBNI derivatives **2**.

diverse processes from **3** to **2** were examined using the MicroKans system by a split-pool strategy. A library of compounds **2** were analyzed by HPLC-MS using UV absorption at 254 nm. Table 1 shows the yields and purity of selected compounds **2** among the combinatorial norBNI library. **2aE**−**jE** were obtained as carboxylic acid derivatives because *tert*-butyl ester was removed under the acidic cleavage conditions. All products were obtained in good purity (68−91%) except for the *p*-methoxybenzyl amino derivatives (56−70% purity). The average purity of all compounds was about 76%.

In conclusion, we have demonstrated an efficient solid-phase synthesis of norBNI derivatives **2** involving interchain coupling reaction of solid-supported ketones **3**. Piloty synthesis using ketones **6** on Wang resin proceeded smoothly to provide the key intermediate **3** in good yield. Combinatorial synthesis of **2** from **3** using 10 aldehydes **4a**−**j** and 11 alkyl halides **5A**−**K** was accomplished by a sprit and pool strategy to provide 120 norBNI derivatives **2** in good purity. This homocoupling solid-phase methodology should be effective for preparing symmetric pyrrole derivatives. Biological assay of the norBNI library is now in progress.

Table 1. Yield and Purity of Selected Compounds **2** among NorBNI Library

entry	aldehyde	halide	norBNI derivative	yield[a] (purity)[b]
1	**4b**		**2b**	39% (81%)
2	**4c**		**2c**	41% (77%)
3	**4d**		**2d**	40% (77%)
4	**4g**		**2g**	55% (74%)
5	**4i**		**2i**	38% (70%)
6	**4e**	**5A**	**2eA**	60% (83%)
7	**4g**	**5A**	**2gA**	55% (71%)
8	**4a**	**5A**	**2aB**	75% (85%)
9	**4d**	**5B**	**2dB**	57% (81%)
10	**4f**	**5B**	**2fB**	68% (82%)
11	**4g**	**5B**	**2gB**	52% (77%)
12	**4i**	**5C**	**2iC**	67% (77%)
13	**4a**	**5D**	**2aD**	47% (72%)
14	**4d**	**5D**	**2dD**	25% (76%)
15	**4g**	**5D**	**2gD**	40% (68%)
16	**4g**	**5E**	**2gE**	63% (79%)[c]
17	**4a**	**5F**	**2aF**	57% (81%)
18	**4f**	**5F**	**2fF**	48% (84%)
19	**4d**	**5G**	**2dG**	49% (75%)
20	**4f**	**5G**	**2fG**	46% (72%)
21	**4h**	**5K**	**2hK**	56% (59%)

[a] Crude yields were estimated on the basis of the weight of recovered crude products. Molecular weights of obtained products were calculated as di-TFA salts. [b] Purity was estimated by HPLC-MS analysis using UV absorption at 254 nm. [c] Yield and purity of **2gE** was estimated as a carboxylic acid derivative.

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Supporting Information Available: Experimental procedures for the solid-phase synthesis and full characterization for compounds **2a**−**d**, **2g**, **2i**, **2aA**, **2eA**, **2gA**, **2aB**, **2dB**, **2fB, 2gB**, **2iC**, **2aD**, **2dD**, **2gD**, **2gE**, **2aF**, **2fF**, **2dG**, **2fG**, and **2hK**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) It was difficult to estimate the purity of the norBNI derivative with two secondary amino groups by reverse-phase HPLC analysis using UV absorption of 254 nm because of its high polarity.

(11) Structural determination of **2a** and **2aA** was achieved by further purification using by preparative LC (column, Inertsil-ODS-3 JET; 20 × 80 mm; flow rate, 10 mL/min; mobile phase, 0.1% HCOOH in H_2O/0.1% HCOOH in MeCN = gradient from 95:5 (0 min) to 50:50 (10 min); UV, 254 nm.).