ORGANIC LETTERS

2009
Vol. 11, No. 3
539−542

Novel Synthesis of a 1,3,5-Trioxazatriquinane Skeleton Using a Nitrogen Clamp

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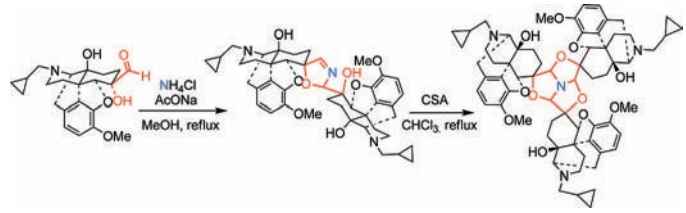
Received October 28, 2008

ABSTRACT



An α-hydroxyaldehyde derived from naltrexone was converted to an oxazoline dimer with ammonium chloride and sodium acetate in MeOH under reflux. The resulting dimer was treated with *dl*-camphorsulfonic acid in $CHCl_3$ to give the trimer. The method for trimer synthesis was also applied to general α-hydroxyaldehydes to afford trimers in good yield.

Naltrexone **1** is a μ opioid receptor antagonist and widely used for therapy of drug addiction. We have been interested in design and synthesis of κ, δ, and ε opioid receptor selective ligands from naltrexone **1** and have successfully synthesized many selective κ, δ, and ε antagonists and agonists.[1] We also reported many new reactions using naltrexone as a starting material.[2] Recently, we have reported that twin drug **2** (Figure 1), which was also prepared from naltrexone **1**, showed ε receptor antagonist activity.[3] In the course of the synthetic investigation of **2**, we found that triplet drug **3** with a 1,3,5-trioxazatriquinane skeleton (highlighted by red and blue colors in Figure 1) was unexpectedly obtained. In this molecule, nitrogen plays an important role in the formation

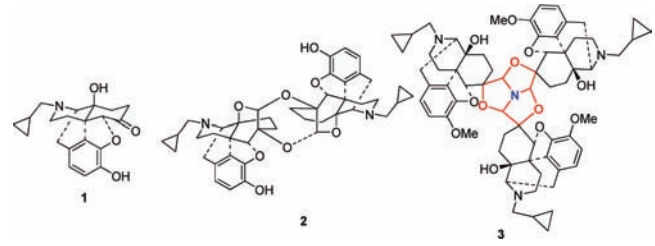


Figure 1. Structures of naltrexone **1**, twin drug **2**, and triplet drug **3** (the 1,3,5-trioxazatriquinane skeleton was highlighted by red and blue colors).

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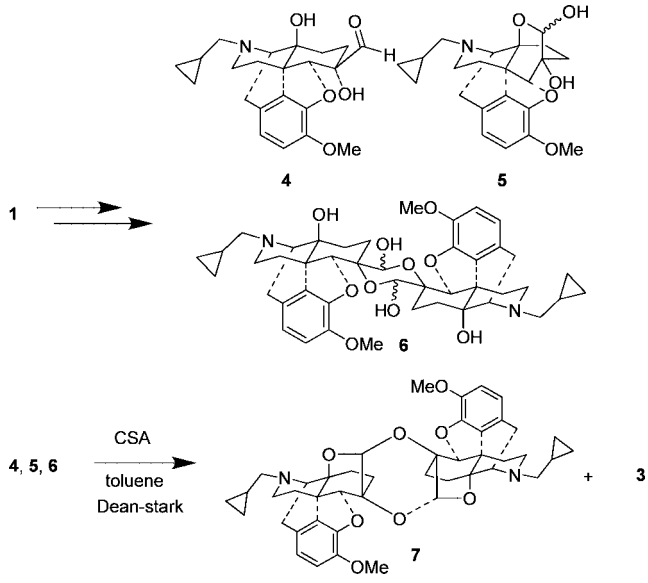
(1) (a) Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 281–282. (b) Portoghese, P. S.; Nagase, H.; Lipkowski, A. W.; Larson, D. L.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 836–841. (c) Portoghese, P. S.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 1344–1347. (d) Portoghese, P. S.; Nagase, H.; Maloney-Huss, K. E.; Lin, C.-E.; Takemori, A. E. *J. Med. Chem.* **1991**, *34*, 1715–1720. (e) Nagase, H.; Hayakawa, J.; Kawamura, K.; Kawai, K.; Takezawa, Y.; Matsuura, H.; Tajima, C.; Endo, T. *Chem. Pharm. Bull.* **1998**, *46*, 366–369. (f) Fujii, H.; Nagase, H. *Curr. Med. Chem.* **2006**, *13*, 1109–1118.

10.1021/ol8024988 CCC: $40.75 © 2009 American Chemical Society
Published on Web 12/30/2008

of the novel skeleton. Nitrogen is a trivalent atom which serves to gather the three molecular units having a keto moiety and to fix them in a precise and rigid fashion as a trimer. Nitrogen acts in a manner analogous to a three-pronged clamp, and we would like to term this phenomenon as a "nitrogen clamp". The nitrogen clamp may be expected to apply the general synthesis of triplet drugs from various ketones which would show unique pharmacological effects. Herein, we report a novel synthetic method for triplet drugs with a rigid 1,3,5-trioxazatriquinane skeleton using a nitrogen clamp.

We have recently reported that acetal dimer **7**, a precursor of the twin drug **2**, was obtained from a mixture of α-hydroxyaldehyde **4**, hemiacetal **5**, and hemiacetal dimer **6** derived from naltrexone **1** in four steps.[3] Examination of the products of the synthesis of acetal dimer **7** revealed novel trimer **3** with the 1,3,5-trioxazatriquinane skeleton in 10% yield, concomitantly with acetal dimer **7** in 13% yield (Scheme 1). At first, the nitrogen source was not clear, but

Scheme 1. Syntheses of Acetal Dimer **7** and Trimer **3**



after a precise search, we determined that the nitrogen was derived from the solvent (saturated ammonia−$CHCl_3$) which was used in preparative TLC for separation of the objective dimer **7**. The structure of trimer **3** was determined by X-ray crystallography (Figure 2). We were interested in the novel structure of **3** and tried to improve the yield of **3** and clarify

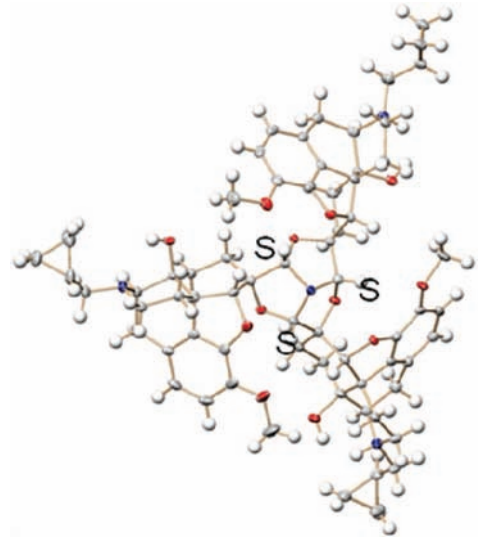
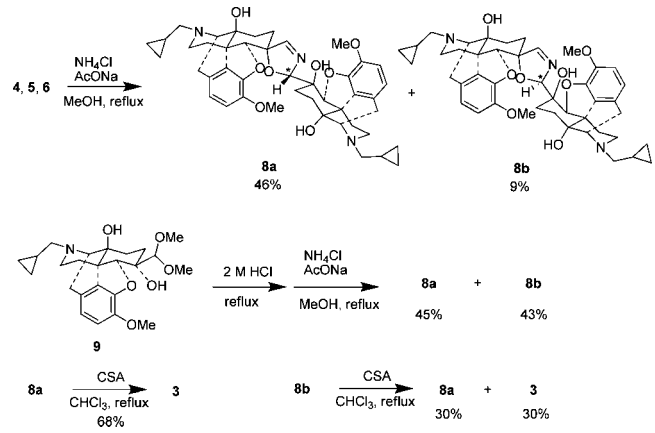


Figure 2. X-ray crystallography of trimer **3**.

the reaction mechanism. When the mixture of compounds **4**, **5**, and **6** was treated with ammonium chloride and sodium acetate in MeOH under reflux, oxazoline dimer **8a** (46%) and its isomer **8b** (9%) were obtained (Scheme 2). Moreover,

Scheme 2. Synthesis of Trimer **3** via Dimer **8**



acetal **9**, which was a precursor of the mixture of compounds **4**, **5**, and **6**, was hydrolyzed with 2 M HCl under reflux, and the resulting mixture (without purification) was treated with ammonium chloride and sodium acetate in MeOH under reflux to afford a mixture of oxazoline **8a** (45%) and its isomer **8b** (43%) (Scheme 2). Dimer **8b** was treated with *dl*-camphorsulfonic acid (CSA) in $CHCl_3$ under reflux to give a mixture of dimer **8a** (30%) and trimer **3** (30%). On the other hand, dimer **8a** was converted to trimer **3** in 68% yield under the same conditions (Scheme 2). These observations supported the idea that dimer **8a** may be the stable isomer and **8b** may be the unstable one, which could be converted to trimer **3** via stable isomer **8a**. Interestingly, X-ray analysis

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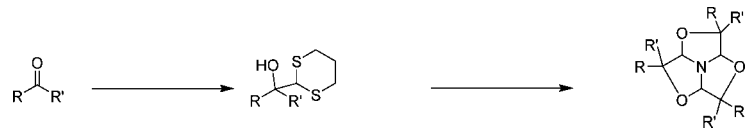
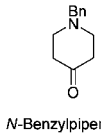
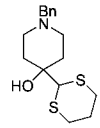
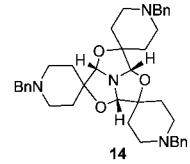
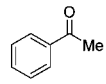
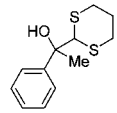
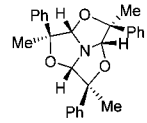
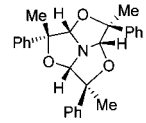
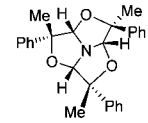
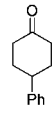
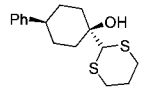
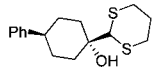
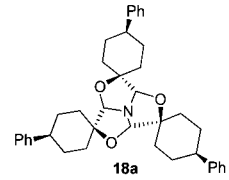
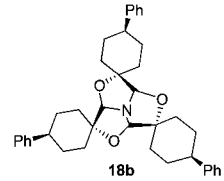
(3) Fujii, H.; Watanabe, A.; Nemoto, T.; Narita, M.; Miyoshi, K.; Nakamura, A.; Suzuki, T.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 438−441.

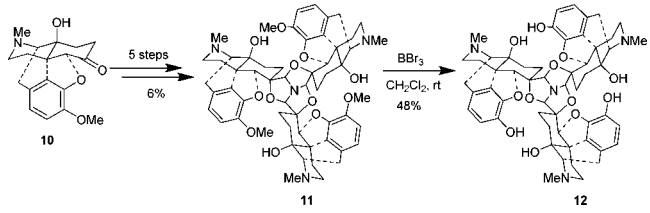
Table 1. General Synthesis of Trimers



run	starting material	intermediate	product	total yield
1	 *N*-Benzylpiperidone	 **13**	 **14**	18%
2	 Acetophenone	 **15**	 **16a** 11%  **16b** 14%  **16c** 10%	35%
3	 4-Phenylcyclohexanone	 **17a**  **17b**	 **18a** 35%  **18b** 13%	48%

showed that the absolute configuration of the three newly formed asymmetric centers of the 1,3,5-trioxazatriquinane moiety in trimer **3** were the all-*S* configurations. The selective formation of the asymmetric centers may be attributed to asymmetric induction by the natural naltrexone skeleton. We also assigned configuration of the * position in dimer **8a** and **8b** as *S* and *R* (Scheme 2), respectively, by 2D NMR spectroscopy. Eventually, *R* configuration isomer **8b** would be the kinetically controlled product, and *S* isomer **8a** would be the thermodynamically controlled one. On the basis of the above considerations, a series of reactions from acetal **9** to trimer **3** were performed without purification to afford **3** in 79% yield. Oxycodone **10** also afforded trimer **11** in 6% total yield (Scheme 3).

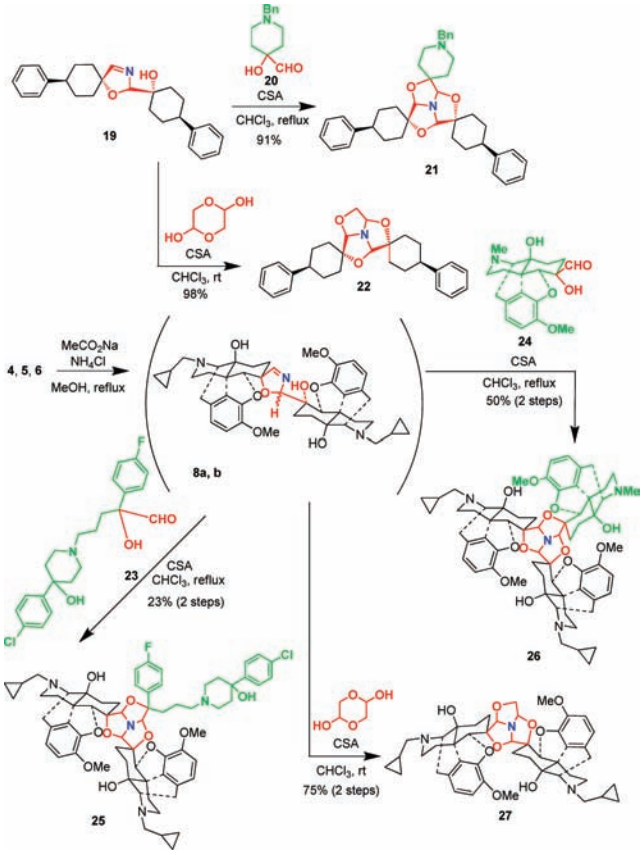
Scheme 3. Synthesis of the *N*-Methyl Trimer



Next, we examined the application of this reaction to model compounds to confirm the generality of the reaction (Table 1). *N*-Benzylpiperidone was converted to trimer **14** in 18% total yield. Acetophenone was converted to a mixture of trimers **16a**, **16b**, and **16c** in 35% total yield. Thioacetals **17a** and **17b**, obtained from 4-phenyl cyclohexanone, were converted to trimer **18a** (35%) and **18b** (13%), respectively.[4] We also tried to apply this reaction to synthesis of a nonsymmetric trimer (Scheme 4). The dimer **19**, prepared from 4-phenylcyclohexanone, was reacted with α-hydroxyaldehyde **20** ($CSA/CHCl_3$, reflux) to afford nonsymmetrical trimer **21** in 91% yield. The dimer **19** was also converted to nonsymmetric trimer **22** with the glycolaldehyde dimer ($CSA/CHCl_3$, rt) in 98% yield. Furthermore, dimers **8a** and **8b**, obtained from a mixture of **4**, **5**, and **6**, were reacted with **23** (derived from haloperidol), **24**, and glycolaldehyde

(4) Determination of the stereochemistry of trimers **14**, **16**, and **18** was described in the Supporting Information.

Scheme 4. Syntheses of Nonsymmetric Trimers



dimer to give nonsymmetric trimer **25**, **26**, and **27** in yields of 23%, 50%, and 75%, respectively. The symmetrical trimer **12**, obtained from oxycodone **10**, showed potent analgesic action in the acetic acid writhing assay (ED_{50} = 0.037 mg/kg) that was about 20 times more potent than that of morphine (ED_{50} = 0.6 mg/kg). The strong analgesic potency may derive from the binding with oligomeric receptor sites.[5]

In conclusion, we have established the first general synthetic method for the trimer with a 1,3,5-trioxazatriquinane skeleton using a nitrogen clamp which could be applied to the synthesis of not only symmetrical trimers but also nonsymmetrical ones. Recent studies have reported that G-protein-coupled receptors (GPCRs) exist as dimers, which may be present as homo- or heterodimers/oligomers. Although the existence of GPCR dimers/oligomers was predicted from early pharmacological and biochemical studies,[5] further evaluations of this phenomenon were impeded by the lack of appropriate reagents.[6] Twin drugs combining two structural components into a single molecule have been described in numerous domains of medicinal chemistry. Symmetrical twin drugs can simultaneously fit to the symmetrical binding sites of the protein complex to afford increased activity. Nonsymmetrical twin drugs, in contrast, may bind to the individual relevant binding sites to give dual action. However, twin drugs can only play one role, either an increase of activity or a dual action. On the other hand, nonsymmetrical triplet drugs which have two of the same moieties and one different substituent may exhibit both increased pharmacological action and dual action because the two identical portions could bind the same receptor sites simultaneously while the third portion could bind a different receptor site or enzyme. Moreover, a symmetrical triplet drug **12** showed 20 times stronger analgesic activity than monomeric compound morphine, suggesting that symmetrical triplet drugs would indicate extremely potent activities. Therefore, the thus obtained trimers with the rigid 1,3,5-trioxazatriquinane skeleton using a nitrogen clamp may be a very useful tool for investigation of oligomeric receptors and enzymes.

Acknowledgment. We acknowledge the Institute of Instrumental Analysis of Kitasato University, School of Pharmacy, for its facilities. We also acknowledge the Uehara Memorial Foundation for financial support.

Supporting Information Available: Experimental procedures, full characterization of compounds, ^{1}H NMR spectra and CIF file of X-ray crystallography of compound **3**, 2D NMR spectra of compounds **8a**, **8b**, and ^{1}H NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8024988

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