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Bioorganic & Medicinal Chemistry 14 (2006) 1339–1347
Bioorganic & Medicinal Chemistry

Stereoselective synthesis and anti-inflammatory activities of 6- and 7-membered dioxacycloalkanes

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Received 30 August 2005; revised 26 September 2005; accepted 26 September 2005
Available online 2 November 2005

Abstract—A class of 5-trifluoroacetylamino-1,3-dioxacycloalkanes, 5-benzoylamino-1,3-dioxacycloalkanes and 5-amino-1,3-dioxacycloalkane compounds were stereoselectively synthesized as potential anti-inflammatory drug candidates. The anti-inflammatory activities of these compounds were tested using the xylene-induced mouse ear edema model, from which multiple compounds possessing anti-inflammatory properties which surpass aspirin were identified; these compounds were then compared to establish structure–activity relationships.

1. Introduction

There has been a long-standing interest to identify novel targets for rational development of anti-inflammatory drugs. Recent studies indicate protein kinase C is a newly identified target for the treatment of inflammatory disorders.[1–9] The inhibition of protein kinase C is a possible point of treatment for various conditions, in particular cancer cells,[10] inflammatory disease,[11] reperfusion injury,[12] and cardiac dysfunction related to reperfusion injury.[9] During recent years, we have been investigating a new class of 2,5-disubstituted-1,3-dioxanes, some of which were found to possess potent anti-inflammatory activity.[13–15] Interestingly, some lead compounds have shown anti-inflammatory properties greater than those of aspirin.[12] This observation has encouraged us to search for new 2,5-disubstituted-1,3-dioxane compounds that possesses better anti-inflammatory activities. Herein, we report the stereoselective synthesis of 6- and 7-membered dioxacycloalkane compounds and their anti-inflammatory activity; the compounds were compared to provide additional information on structure–activity relationship, particularly on the roles of both substituents and stereochemistry features of the ring structures.

2. Results and discussion

We had previously described 1,3-dioxacycle derivatives prepared through the trans-acetalization of 1,1,3,3-tetramethoxypropane and aminodiols,[13–15] which can be easily prepared from a naturally optically active amino acid. Our original approach was to engage the pre-existing stereocenter of the chiral aminodiols to direct the subsequent trans-acetalization reaction. In fact, our previous work demonstrated that the stereochemistry of the ring formed in the trans-acetalization reaction was indeed dependent on the structure of the aminodiol compounds.[13–15]

The synthetic routes used to prepare optically active aminodiols are outlined in Scheme 1. The key intermediates, aminodiols **3a**–**c**, were easily achieved via esterification of optically active amino acids in the presence of thionyl chloride and methanol, followed by reduction with KBH_4. The stereochemistry of the aminodiols

Keywords: Stereoselective trans-acetalization; 5-Amino-dioxacycloalkanes; Anti-inflammatory activity.
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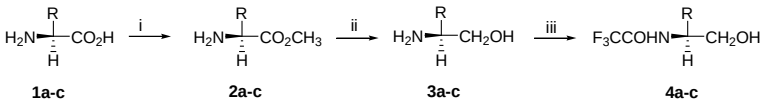
doi:10.1016/j.bmc.2005.09.068



Scheme 1. Synthetic route to compound **4a**–**c**. Reagents and conditions: (i) $SOCl_2$/MeOH, 0 °C to rt; (ii) KBH_4/THF, rt; (iii) TFA. In **1a**–**3a**: R = CH_2OH; **1b**–**3b**: R = $CH(CH_3)OH$; **1c**: R = CH_2CO_2H; **2c**: R = $CH_2CO_2CH_3$; **3c**: R = CH_2CH_2OH. In **4a**: R = CH_2OH; **4b**: R = $CH(CH_3)OH$; **4c**: R = CH_2CH_2OH.

was confirmed through conversion to the corresponding 2-trifluoroacetylamino-1,3-propanediols (**4a**–**c**), in which **4b** and **c** are enantiomerically pure.

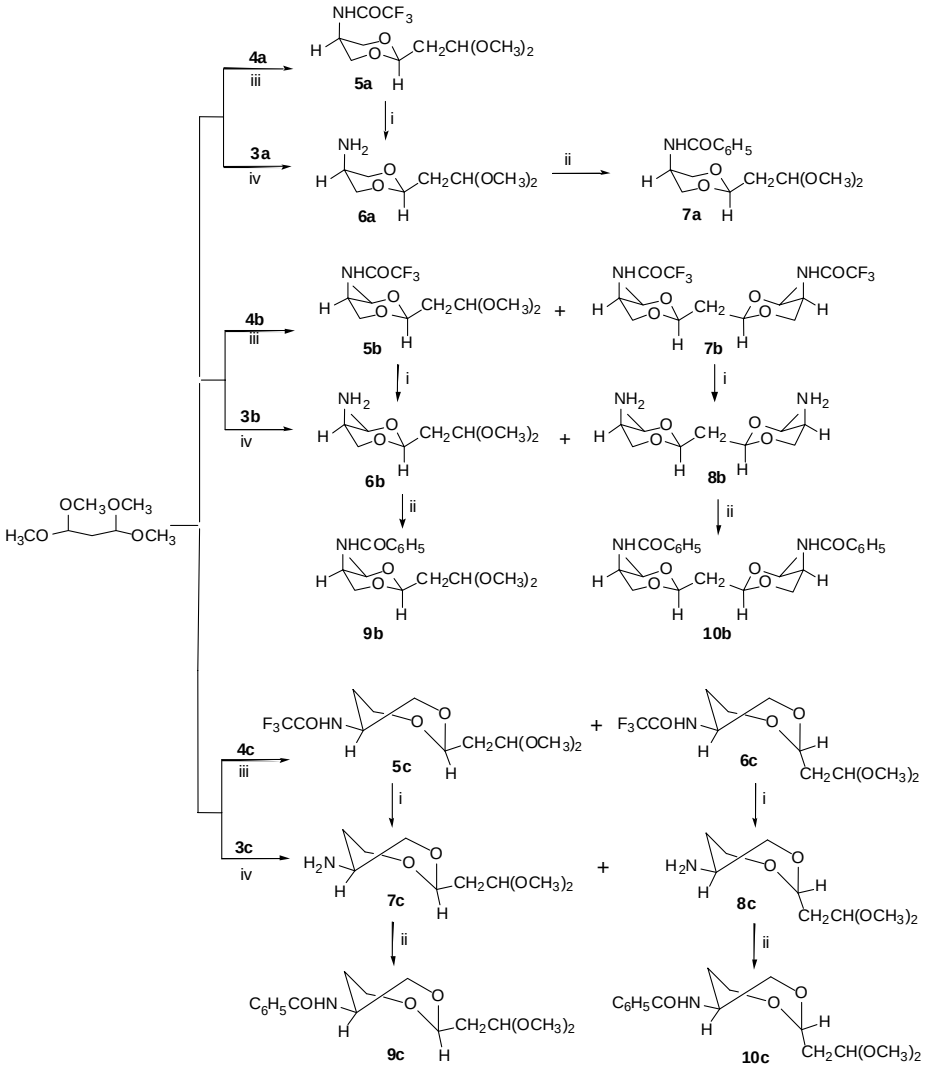
Our previous work described the trans-acetalization of phenylacetaminodiols and equal amount of the 1,1,3,3-tetramethoxypropane gave a complex mixture of products composed of both *cis*- and *trans*-2,5-disubstituted-1,3-dioxamonocycloalkanes, and both *cis*- and *trans*-2,5-disubstituted-1,3-dioxabiscycloalkanes.[13] To our surprise, when **3a** was treated with 1,1,3,3-tetramethoxypropane, the trans-acetalization of **3a** exclusively gave *cis*-**6a**. The more sterically demanding trans- and dicyclic products were not observed. Neither increasing the number of equivalents of either the starting reaction compounds nor changing the reaction conditions (e.g., catalysts and reaction temperature) had an appreciable effect on the conversion. After screening several Lewis acids, trimethylsilyl chloride was found to provide the highest yields for this trans-acetalization (64% yield). Similarly, the trans-acetalization of **4a** with 1,1,3,3-tetramethoxypropane gave *cis*-**5a** as the sole product, and both *trans*- and dicyclic products were not observed.

Through nuclear overhauser effect (NOE) difference experiments, both **5a** and **6a** exhibited no positive NOE signal between the functionality at the 2- and 5-positions. We hypothesized that this is due to the rapid exchange of hydrogens between both the 2′-amine and 2′-aminotrifluoroacetyl moieties with $CHCl_3$-*d* solvent, resulting in the hydrogens unable to participate in subsequent NOE experiment. Therefore, **6a** was converted to **7a** to enable a benzoyl functionality on the 5′-NH_2 group, which will thus stabilize the hydrogen atom for participation in the NOE difference spectra. Consequently, a positive NOE effect was observed for **7a** between the NH at the 5-position and CH_2 at the 2-position, indicating that the two substituents on the ring are arranged in a *syn*-configuration. To ensure correct structural assignment to **5a**, the compound was then subjected to saponification to afford **6a**. Based on the configuration of **7a**, the substituents at both 2- and 5-positions of **5a** and **6a** were consequently assigned to be in a *syn*-arrangement (Scheme 2).

Under similar condition, the trans-acetalization of **3b** with 1,1,3,3-tetramethoxypropane afforded **6b** and **8b** in 78% and 8% yield, respectively. To assign the stereochemistry of **6b** and **8b**, both compounds again underwent benzoylacetylation reactions to afford **9b** and **10b**, respectively. For both **9b** and **10b**, a positive NOE effect was subsequently observed between the substituents at the 2-, 4-, and 5- positions, which indicate that both the substituents on the rings of **9b** and **10b** are in *syn*-arrangement (Scheme 2). Based on the configuration of **9b** and **10b**, the substituents at the 5-, 4-, and 2- positions on the ring of **6b** and **8b** were assigned to be in *syn*-arrangement. The trans-acetalization reaction of **4b** with 1,1,3,3-tetramethoxypropane provides **5b** and **7b** in 63% and 11% yield, respectively. This reveals a similar trend of stereoselectivity with **3b** in the trans-acetalization reactions. Determining the configuration of **5b** and **7b** was again performed via saponification of **5b** and **7b** to **6b** and **8b**. Based on the configuration of **6b** and **8b**, the substituents at the 5-, 4-, and 2- positions on the ring of **5b** and **7b** were consequently assigned to be in a *syn*-arrangement. These observations imply that simple 5-substituted 1,3-dioxanes are effective as chiral auxiliaries for controlling stereoselectivity in their subsequent trans-acetalization reactions. The dicyclic products consistently adopt a 2,5-*cis*-configuration, which indicatesthe second trans-acetalization reaction to be highly stereoselective (Scheme 2).

However, treatment of **4c** and 1,1,3,3-tetramethyoxylpropane under conditions similar to those used for **4b** gave different results. No dicyclic product, but only 1:1 mixture of *cis*- and *trans*-monocycle (**5c**/**6c**), were observed. In a similar manner, the trans-acetalization of **3c** and 1,1,3,3-tetramethyoxypropane gave **7c**, and **8c** in 31% and 15% yield, respectively (Scheme 2). From NOE difference experiments performed on **5c**, **6c**, **7c** and **8c**, no positive NOE signal was observed between the NH_2 at the 5-position and CH_2 at the 2-position, again presumably due to the hydrogen rapid exchange with $CHCl_3$-*d*. Thus, to confirm the stereochemistry of **7c** and **8c**, the compounds were converted into **9c** and **10c**, respectively. For **9c**, a positive NOE effect was observed between the substitutions at 2- and 5-position, indicating that substitutions on the ring of **9c** are in a *syn*-arrangement. For **10c**, no NOE effect was observed between the substitutions at the 2- and 5-positions, indicating the configuration of **10c** is in a trans-arrangement. To ensure the configuration of **5c** and **6c**, they were subjected to saponification to **7c** and **8c**. Consequently, based on the configuration of **9c** and **10c**, the substitutions on the ring of **5c** and **7c** were assigned in *syn*-arrangement, and those of **6c** and **8c** were assigned to be in trans-arrangement (Scheme 2).

We had previously described that trans-acetalization of *N*-benzoyl derivatized **3a**–**c** with 1,1,3,3-tetramethoxypropane provided isomeric mixtures composed of *cis*-monocyclic and *trans*-*cis*-dicyclic dioxacyclohexane products.[10] In this paper, an interesting observation is the high stereoselectivity afforded through the substituents on the ring. In addition, it is worth noting that the ratios of the cis- to trans-product and the



Scheme 2. Synthetic route to compounds **5a–c**, **6a–c**, **7a–c**, **8a–c**, **9a–c**, and **10a–c**. Reagents and conditions: (i) NaOH (aq)/EtOH; (ii) PhCOCl/TEA, $CHCl_3$, 0 °C to rt; (iii) concentrated HCl (cat), EtOAc, rt; (iv) trimethylsilyl chloride (cat), DMF, rt.

monocyclic to dicyclic product are significantly dependent on the ring size formed via the trans-acetalization of aminodiol. For example, the trans-acetalizations of **4a** (namely, *N*-trifluoroacetyl derivatized **3a**) and 1,1,3,3-tetramethoxypropane exclusively provided *cis*-monocycle (**5a**). Under similar condition, the trans-acetalizations of **4b** (namely, *N*-trifluoroacetyl derivatized **3b**) and 1,1,3,3-tetramethoxypropane provided a pair of *cis*-monocycle and *cis*-*cis*-dicycle (**5b/7b**) in 6:1 ratio. On the contrary, the trans-acetalizations of **4c** (namely, *N*-trifluroacetyl derivatized **3c**) and 1,1,3,3-tetramethoxypropane provided a pair of *cis*- and *trans*-monocycle (**5c/6c**) in 1:1 ratio, and no bicylic compounds were observed. Furthermore, it was observed that the trans-acetalization stereoselectivity trend was affected accordingly to the bulkiness of the substituent at the 5-position. When aminotrifluoroacetyl was replaced with amine moiety, the trans-acetalizations of **3a** with 1,1,3,3-tetramethoxypropane exclusively provided *cis*-monocycle **6a**. The trans-acetalizations of **3b** with 1,1,3,3-tetramethoxypropane provided a pair of *cis*-monocycle and *cis*-*cis*-dicycle (**6b/8b**) in 10:1 ratio, while the trans-acetalizations of **3c** and 1,1,3,3-tetramethoxypropane provided a pair of *cis*- and *trans*-monocycle (**7c/8c**) in 2:1 ratio.

The anti-inflammatory activities of all of the synthesized compounds were evaluated using a xylene-induced ear edema model assay.[15,16] Each compound was initially tested at a dose of 20 mg/kg. The starting compounds, aminodiols, **3a–c**, were first assessed to confirm the necessity of 1,3-dioxane ring for anti-inflammation activity. Observation that both aminodiols were ineffective as anti-inflammatory compounds suggested that the rigid 1,3-dioxacycle ring should be retained. This observation was consistent with our previously reported results.[15] The efficacy of the 7-membered ring in a variety of drugs, for example, benzodiazapenes, is believed to be due to its modest degree of structural flexibility that permits receptor-induced fit, which might lead to an improved biological profile.[17] However, the anti-inflammatory activities of the compounds containing 7-membered dioxacycloalkanes (**5c**: 44.5%; **7c**: 67.3%; **9c**: 48.5%) are slightly decreased

over those of their corresponding 6-membered compounds (**5b**: 50.8%; **6b**: 71.1%; **9b**: 51.3%). Moreover, stereochemical features of the 7-membered dioxcycloalkanes do not appear to play any roles in the biological profile since the corresponding trans-compounds (**6c**: 43.3%; **8c**: 62.6%; **10c**: 45.6%) displayed comparable anti-inflammatory activity compared to cis-compounds (**5c**: 44.5%; **7c**: 67.3% **9c**: 48.5%). Compared with monocyclic acetal (**5b**: 50.8%; **6b**: 71.1%; **9b**: 51.3%), dicyclic acetal (**7b**: 48.7%; **8b**: 69.1%; **10b**: 47.0%) exhibited a slightly decreased anti-inflammatory activity. This is possible partly due to the overall size of the monocyclic acetals (as it is smaller than that of dicyclic acetals), which will occupy a smaller volume space and thereby avoiding steric interactions during receptor binding.

Introduction of amino moiety to the 5-position of 1,3-dioxane, namely compounds, **6a**,**b**, **7c**, and **8b**,**c**, all exhibited significant improvements of the anti-inflammatory activity. This observation suggests that the amino group is optimal for the anti-inflammatory potency. A minor structural alteration can lead to a marked change in anti-inflammatory activity, which implies that the improved biological profile might result from a synergic effect. Nevertheless, the formation of the hydrogen bond with the amino moiety might be critical during the receptor binding process; we strongly suspect the better anti-inflammatory activity of compound results from facile protonation of the amine moieties, which, in turn, enable the molecule to easily access cellular membrane.

In the in vivo assay, the suspension of the tested compound in 0.5% carboxymethyl cellulose (CMC) was orally administered. From Table 1, it was noted that the most potent compounds (**6a**,**b**, **7c**, and **8b**,**c**) all exhibited anti-inflammatory activities higher than that of than the standard reference drug in aspirin. The ear edema inhibition for the above-mentioned five compounds at the dose of 20 mg/kg, is calculated to be 73.6%, 71.1%, 69.1%, 67.3% and 62.6%, respectively, compared with that of aspirin 46.3%. Therefore, they were subsequently administered in a series of lower concentration doses to enable a detailed pharmacological activity profile (data summarized in Table 2).

Oral administration of compounds **6a**,**b**, **7c**, and **8b**,**c** is observed to all produce a dose-dependent anti-inflammatory response in the xylene-induced mouse ear edema test. For compound **6a** at doses of 0.8, 4.0, and 20.0 mg/kg, the anti-inflammatory effect was observed to be 10.4%, 48.5%, and 73.6%, respectively. Thus, **6a** demonstrated a significant enhancement in its anti-inflammatory activity with doses above 4.0 mg/kg. Aspirin, by comparison, has anti-inflammatory effect of 46.3% at a dose of 30 mg/kg. Similarly, the anti-inflammatory activity for compound **6b** was 8.38%, 44.2%, and 71.1%, at doses of 0.8, 4.0, and 20.0 mg/kg, respectively. Compound **6b** exhibited comparable anti-inflammatory activity with aspirin at a dose of 4.0 mg/kg. Therefore, compounds **6a**,**b**, **7c**, and **8b**,**c** exhibited dose-dependent anti-inflammatory action.

Table 1. Anti-inflammatory activities of 6- and 7-membered dioxacycloalkanes against xylene-induced ear edema in mice

Agents	Anti-inflammatory activity	
	Edema weight ($X \pm$ SD mg)	Inhibition (%)
CMC	7.76 ± 1.55	N
Aspirin	4.17 ± 1.80[a]	46.3
TMPA	8.30 ± 1.87	N
3a	8.11 ± 1.89	N
3b	8.20 ± 1.99	N
3c	7.58 ± 1.86	N
5a	3.75 ± 1.69[a]	51.7
6a	2.05 ± 1.50[a,b,g]	73.6
7a	3.62 ± 1.88[a]	53.4
5b	3.82 ± 1.73[a]	50.8
6b	2.24 ± 1.65[a,c,g]	71.1
7b	3.98 ± 1.82[a]	48.7
8b	2.40 ± 1.83[a,d,g]	69.1
9b	3.78 ± 1.77[a]	51.3
10b	4.11 ± 1.90[a]	47.0
5c	4.31 ± 1.75[a]	44.5
6c	4.40 ± 1.72[a]	43.3
7c	2.54 ± 1.78[a,e,g]	67.3
8c	2.90 ± 1.75[a,f,g]	62.6
9c	4.00 ± 1.46[a]	48.5
10c	4.22 ± 1.85[a]	45.6

N = no inhibition.
Dose of aspirin = 30 mg/kg; dose of the synthesized compounds = 20 mg/kg; TMPA = 1,1,3,3-tetramethoxypropane; $n = 11$.
[a] Compared to CMC, TMPA, and **3a**–**c**, $p < 0.001$.
[b] Compared to **5a** and **7a**, $p < 0.05$.
[c] Compared to **5b** and **9b**, $p < 0.05$.
[d] Compared to **7b** and **10b**, $p < 0.05$.
[e] Compared to **9c**, $p < 0.05$.
[f] Compared to **10c**, $p < 0.05$.
[g] Compared to aspirin, $p < 0.05$.

Table 2. Anti-inflammatory activities of **6a**,**b**, **7c**, and **8b**,**c** at different doses against xylene-induced ear edema in mice

Agents	Dose (mg/kg)	Edema weight ($X \pm$ SD mg)	Inhibition (%)
6a	20.0	2.05 ± 1.50[a]	73.6
6b	20.0	2.24 ± 1.65[a]	71.1
8b	20.0	2.40 ± 1.83[a]	69.1
7c	20.0	2.54 ± 1.78[a]	67.3
8c	20.0	2.90 ± 1.75[a]	62.6
6a	4.0	4.00 ± 1.69[b]	48.5
6b	4.0	4.33 ± 1.95[b]	44.2
8b	4.0	4.60 ± 1.61[a]	40.7
7c	4.0	5.08 ± 1.51[a]	34.5
8c	4.0	5.39 ± 1.87[a]	30.5
6a	0.8	6.95 ± 1.55	10.4
6b	0.8	7.11 ± 1.70	8.38
8b	0.8	7.35 ± 1.80	N
7c	0.8	7.60 ± 1.82	N
8c	0.8	7.79 ± 1.80	N

N = no inhibition.
[a] Compared to 4.0 mg/kg group, $p < 0.01$.
[b] Compared to 0.8 mg/kg group, $p < 0.01$.

3. Conclusion

It was observed that 6- and 7-membered dioxacycloalkanes significantly inhibited xylene-induced inflammation in mice when compared with the control in aspirin. The

potencies of 5-trifluoroacetylamino dioxacycloalkanes (**5a**–**c**, **6c**, and **7b**), 5-benzoylamino dioxacycloalkanes (**7a**, **9b**,**c** and **10b**,**c**), and the standard reference drug in aspirin are highly similar. In particular, 5-amino-dioxacycloalkanes (**6a**,**b**, **7c**, and **8b**,**c**) exhibited anti-inflammatory activities higher than that of aspirin. Though the size and stereochemical specificities of these 1,3-dioxanes exhibited little effect on the anti-inflammatory activities, the availability of positive charge at the 5-position is observed to exhibit significant effect on its resulting anti-inflammatory activity. This observation implies that the anti-inflammatory activity of 1,3-dioxane compounds is partly dependent on their ability to penetrate cell membrane. Interestingly, the anti-inflammatory activity of 5-amino-dioxacycloalkanes (**6a**,**b**, **7c**, and **8b**,**c**) after oral administration to mice is similar to that of aspirin, suggesting that this class of compounds could be employed as a model system for future development of new anti-inflammatory agents.

4. Experimental

4.1. General

Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. Unless otherwise stated, all reactions were performed under a nitrogen atmosphere (1 bar). The agents used in this work were purchased from Sigma Chemical Co (USA). Chromatography was performed on Qingdao silica gel H (Qingdao of China). The purities of the intermediates and the products were confirmed by TLC (Merck silica gel plates of type 60 F_{254}, 0.25 mm layer thickness, Germany) and HPLC (Waters, C_{18} column 4.6×150 mm, USA). NMR spectra were recorded at 300 MHz on a VXR-300 instrument or at 500 MHz on a Bruker Am-500 instrument in $CDCl_3$ with tetramethylsilane as internal standard. EI-MS was determined by Trace MS System (Thermo Finnigan, USA). Optical rotations were determined with a Schmidt and Haensch Polartromic D instrument (Germany). Statistical analysis of all the biological data was carried out by use of ANOVA test, $p < 0.05$ being considered significant.

4.2. 2-Amino-1,3-propanediol (3a)

To a mixture of SO_2Cl (30 ml, 0.42 mol) in 200 ml of methanol, L-Ser (21.0 g, 0.2 mol) was added dropwise at 0–5 °C. The reaction was allowed to proceed at 25 °C with stirring overnight, until TLC ($CHCl_3$/CH_3OH, 30:1) indicated complete disappearance of L-Ser. The solvent was removed in vacuo to yield HCl·L-Ser-OMe (**2a**) (36.0 g). HCl·L-Ser-OMe was then dissolved in 500 ml (95%) of ethanol, to which the solution of potassium borohydride (46.0 g, 0.85 mol) in 165 ml water was added dropwise with stirring. The reaction mixture was then stirred at room temperature for another 12 h. Subsequent TLC (C_2H_5OH/H_2O, 7:3) indicated complete disappearance of **2a**. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to 50 ml. At 0 °C, 60 ml of concentrated hydrochloric acid was slowly added to the filtrate over 1 h. The reaction mixture was treated with aqueous solution of sodium hydroxide (20%) to ~pH 10. The mixture was extracted with chloroform and evaporated to provide 11.3 g (62%) of the title compound as a colorless powder. Mp 55–58 °C. FAB-MS *m*/*z* (%): 92 $[M+H]^+$. ^1H NMR (DMSO-d_6, δ): 2.02 (s, 2H), 2.13 (s, 2H), 2.63 (m, $J = 5.8$ Hz, 1H), 3.18 (q, $J = 5.5$ Hz, 2H), 3.28 (q, $J = 5.2$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ): 54.64, 63.63. Anal. calcd for $C_3H_9NO_2$: C, 39.95; H, 9.96; N, 15.37. Found: C, 40.14; H, 10.11; N, 15.29.

4.3. (2*R*,3*R*)-2-Amino-3-methyl-1,3-butanediol (3b)

Using the same procedure as that for preparation of **3a** starting from L-Thr (30.0 g, 0.252 mol), the title compound was obtained as a colorless powder 15.4 g (58%). Mp 50–52 °C. FAB-MS *m*/*z* (%): 106 $[M+H]^+$. ^1H NMR (DMSO-d_6, δ): 1.01 (d, $J = 6.3$ Hz, 3H), 2.03 (s, 2H), 2.14 (s, 2H), 2.37 (m, $J = 3.3$ Hz, 1H), 3.19 (q, $J = 5.7$ Hz, 1H), 3.35 (q, $J = 5.7$ Hz, 1H), 3.47 (q, $J = 4.2$ Hz, 1H). ^{13}C NMR (DMSO-d_6, δ): 20.23, 58.32, 63.60, 66.78. $[\alpha]_D^{20}$ −4.0 (*c* 4, H_2O). Anal. calcd for $C_4H_{11}NO_2$: C, 45.70; H, 10.55; N, 13.32. Found: C, 45.59; H, 10.46; N, 13.50.

4.4. (2*S*)-2-Amino-1,4-butanediol (3c)

Using the same procedure as that for preparation of **3a** starting from L-Asp (12.0 g, 0.1 mol), 7.3 g (39%) of the title compound was obtained as a colorless oil. FAB-MS *m*/*z* (%): 106 $[M+H]^+$. ^1H NMR (DMSO-d_6, δ): 1.25 (m, $J = 4.3$ Hz, 1H), 1.48 (m, $J = 3.4$ Hz, 1H), 2.03 (s, 2H), 2.13 (s, 2H), 2.69 (m, $J = 2.4$ Hz, 1H), 3.11 (q, $J = 5.7$ Hz, 1H), 3.24 (q, $J = 5.1$ Hz, 1H), 3.48 (t, $J = 6.5$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ): 36.45, 50.96, 58.99, 66.98. $[\alpha]_D^{20}$ −13.5 (*c* 4, H_2O). Anal. calcd for $C_4H_{11}NO_2$: C, 45.70; H, 10.55; N, 13.32. Found: C, 45.88; H, 10.70; N, 13.20.

4.5. 2-Fluoroacetylamino-1,3-propanediol (4a)

The mixture of 273 mg (3.0 mmol) of **3a**, 930 g (6.6 mmol) of ethyl trifluoroacetate, and 6 ml of anhydrous THF was stirred at room temperature for 24 h, and TLC ($CHCl_3$/MeOH, 10:3) indicated complete disappearance of **3a**. To the reaction mixture, 500 mg of sodium bicarbonate was added and stirred at room temperature for another 1 h. The reaction mixture was filtered, the filtrate was evaporated, and the residue was dissolved in 25 ml chloroform. The solution was washed with water (3×10 ml) and the organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was evaporated to provide 539 mg (96%) of the title compound as a colorless powder. Mp 60–62 °C. FAB-MS *m*/*z* (%): 188 $[M+H]^+$. ^1H NMR (DMSO-d_6, δ): 2.04 (s, 2H), 3.43 (m, $J = 5.9$ Hz, 1H), 3.57 (q, $J = 5.4$ Hz, 2H), 3.58 (q, $J = 5.4$ Hz, 2H), 8.01 (s, 1H). ^{13}C NMR (DMSO-d_6, δ): 58.62, 65.70, 125.12, 169.88. Anal. calcd for $C_5H_8F_3NO_3$: C, 32.09; H, 4.31; N, 7.49. Found: C, 32.24; H, 4.19; N, 7.32.

4.6. (2*R*,3*R*)-2-Fluoroacetylamino-3-methyl-1,3-butanediol (4b)

Using the same procedure as that for preparation of **4a**, starting from 315 mg (3.0 mmol) of **3b**, 585 mg (97%) of the title compound were obtained as a colorless powder. Mp 71–72 °C. FAB-MS *m*/*z* (%): 202 $[M+H]^+$. ^1H NMR (DMSO-d_6, δ): 1.22 (d, J = 6.4 Hz, 3H), 2.05 (s, 2H), 3.59 (m, J = 3.5 Hz, 1H), 3.60 (q, J = 5.5 Hz, 1H), 3.66 (q, J = 5.5 Hz, 1H), 3.67 (q, J = 4.3 Hz, 1H), 8.00 (s, 1H). ^{13}C NMR (DMSO-d_6, δ): 17.15, 58.45, 62.61, 68.26, 125.58, 169.87. $[\alpha]_D^{20}$ −4.7 (*c* 4, H_2O). Anal. calcd for $C_6H_{10}F_3NO_3$: C, 35.83; H, 5.01; N, 6.96. Found: C, 35.69; H, 4.89; N, 6.85.

4.7. (2*S*)-2-Fluoroacetylamino-1,4-butanediol (4c)

Using the same procedure as that for preparation of **4a**, starting from 315 mg (3.0 mmol) of **3c**, 579 mg (96%) of the title compound were obtained as colorless oil. FAB-MS *m*/*z* (%): 202 $[M+H]^+$. ^1H NMR (DMSO-d_6, δ): 1.63 (m, J = 4.5 Hz, 1H), 1.68 (m, J = 3.6 Hz, 1H), 2.10 (s, 2H), 3.48 (m, J = 2.6 Hz, 1H), 3.50 (q, J = 5.8 Hz, 1H), 3.64 (q, J = 5.3 Hz, 1H), 3.70 (t, J = 6.3 Hz, 2H), 8.00 (s, 1H). ^{13}C NMR (DMSO-d_6, δ): 35.33, 46.64, 57.88, 69.11, 125.55, 168.98. $[\alpha]_D^{20}$ −12.9 (*c* 4, H_2O). Anal. calcd for $C_6H_{10}F_3NO_3$: C, 35.83; H, 5.01; N, 6.96. Found: C, 36.91; H, 5.14; N, 6.82.

4.8. (*cis*)-2-(2,2-Dimethoxyethyl)-5-trifluoroacetylamino-1,3-dioxacyclohexane (5a)

To the solution of 561 mg (3.0 mmol) of **4a** in 8 ml of ethyl acetate, 520 mg (3.17 mmol) of 1,1,3,3-tetramethylpropane and 0.09 ml of concentrated hydrochloric acid were added. The reaction mixture was stirred at room temperature for 24 h and TLC ($CHCl_3$/MeOH, 20:1) indicated complete disappearance of **4a**. The reaction mixture was treated with 0.09 ml of ammonia spirit and evaporated to provide 319 mg (37%) of the title compound as colorless oil. FAB-MS *m*/*z* (%): 288 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.92 (t, J = 5.5 Hz, 2H), 3.28 (s, 6H), 3.76 (m, J = 4.5 Hz, 1H), 4.12 (d, J = 4.3 Hz, 2H), 4.12 (q, J = 4.3 Hz, 2H), 4.20 (t, J = 5.6 Hz, 1H), 4.68 (t, J = 5.6 Hz, 1H), 8.09 (s, 1H). ^{13}C NMR ($CDCl_3$, δ): 41.61, 48.00, 51.59, 72.37, 93.88, 96.39, 125.55, 170.55. Anal. calcd for $C_{10}H_{16}F_3NO_5$: C, 41.82; H, 5.61; N, 4.88. Found: C, 41.68; H, 5.79; N, 4.70.

4.9. [(*cis*)-2-(2′,2′-Dimethoxylethyl)-1,3-dioxan-5-yl]-amine (6a)

(A) To the solution of 861 mg (3.0 mmol) of **5a** in 15 ml water, 15 ml ethanol and 600 mg NaOH were added. The solution was stirred at room temperature for 3 h and TLC ($CHCl_3$/MeOH, 10:1) indicated complete disappearance of **5a**. To the solution, 1 ml of concentrated hydrochloric acid was added dropwise at 0 °C to pH 7.0. The reaction mixture was evaporated under reduced pressure and the residue was extracted with chloroform (3 × 15 ml). The organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by chromatography on silica ($CHCl_3$/MeOH, 15:1) to provide 556 mg (97%) of the title compound.

(B) The solution of 273 mg (3.0 mmol) of **3a**, 2 ml of anhydrous ethanol was stirred at 0 °C and adjusted to pH 4 with hydrochloric acid. The solution was evaporated and the residue was mixed with 5 ml of anhydrous DMF, 510 mg (3.11 mmol) of 1,1,3,3-tetramethoxylpropane, and 700 mg of trimethylsilyl chloride. The reaction mixture was stirred at room temperature for 24 h and TLC ($CHCl_3$/MeOH, 10:1) indicated complete disappearance of **3a**. The reaction mixture was treated with ammonia to pH 9.0 and then filtered. The filtrate was evaporated and the residue was dissolved in 2 ml water. The solution was extracted with chloroform (3 × 5 ml) and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated and the residue was purified by silica gel chromatography ($CHCl_3$/MeOH, 15:1) to provide 367 mg (64%) of the title compound. FAB-MS *m*/*z* (%): 192 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.85 (s, 2H), 1.92 (t, J = 5.7 Hz, 2H), 2.66 (m, J = 1.5 Hz, 1H), 3.28 (s, 6H), 3.82 (q, J = 4.3 Hz, 2H), 3.89 (q, J = 4.3 Hz, 2H), 4.51 (t, J = 6.0 Hz, 1H), 4.59 (t, J = 5.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ): 38.31, 45.76, 52.98, 72.74, 99.85, 100.95. Anal. calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.18; H, 8.79; N, 7.44.

4.10. *N*-[(*cis*)-2-(2′,2′-Dimethoxylethyl)-1,3-dioxan-5-yl]benzoylamine (7a)

To the solution of 91 mg (0.48 mmol) of **6a** at 0 °C, 49 mg (0.48 mmol) of triethylamine and 3 ml chloroform 67 mg (0.48 mmol) of benzoyl chloride were added dropwise. The reaction mixture was stirred at room temperature for 3 h and TLC ($CHCl_3$/MeOH, 20:1) indicated complete disappearance of **6a**. The reaction mixture was evaporated and the residue was dissolved in 3 ml ether. The solution was stirred at room temperature for 1 h and then filtered. The filtrate was evaporated and the residue was purified by silica gel chromatography ($CHCl_3$/MeOH, 15:1) to provide 138 mg (98%) of the title compound as a colorless powder. Mp 140–142 °C. FAB-MS *m*/*z* (%): 296 $[M+H]^+$. IR (KBr, cm^{-1}) *v*: 3264, 3052, 2920, 2851, 1621, 1601, 1570, 1545, 1446, 1381, 1364, 1190, 1074, 718, 697. ^1H NMR ($CDCl_3$, δ): 1.98 (t, J = 7.89 Hz, 2H), 3.34 (s, 6H), 4.04 (d, J = 12.5 Hz, 4H), 4.10 (m, J = 9.5 Hz, 1H), 4.56 (t, J = 6.3 Hz, 1H), 4.74 (t, J = 6.3 Hz, 1H), 7.45 (d, J = 11.0 Hz, 2H), 7.52 (t, J = 11.0 Hz, 1H), 7.83 (t, J = 11.0 Hz, 2H). In a NOESY experiment, a NOE between the NH at the 5-position and the CH_2 at the 2-position was observed. Anal. calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.15; H, 7.01; N, 4.66.

4.11. (2*S*,4*R*,5*R*)-2-(2,2-Dimethoxylethyl)-4-methyl-1,3-dioxan-5-yl-trifluoroacetylamine (5b) and *N*,*N*′-methylenebis[(2*S*,4*R*,5*R*)/(2*R*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bistrifluoroacetylamine (7b)

Using the same procedure as that for the preparation of **5a**, starting from **4b** (603 mg, 3.0 mmol), 570 mg (63%) of **5b** and 145 mg (11%) of **7b** was obtained as a colorless powder.

Compound **5b**: mp 114–116 °C. FAB-MS *m*/*z* (%): 302 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.22 (d, $J = 5.8$ Hz, 3H), 1.88 (m, $J = 6.0$ Hz, 2H), 3.24 (s, 6H), 3.76 (m, $J = 2.6$ Hz, 1H), 4.01 (d, $J = 2.6$ Hz, 2H), 4.18 (t, $J = 6.0$ Hz, 1H), 4.58 (m, $J = 5.8$ Hz, 1H), 4.69 (t, $J = 5.6$ Hz, 1H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$,δ): 15.69, 41.94, 48.10, 56.18, 69.77, 71.70, 91.38, 96.39, 125.55, 170.58. $[\alpha]_D^{20}$ −7.8 (*c* 2.0, $CHCl_3$). Anal. calcd for $C_{11}H_{18}F_3NO_5$: C, 43.86; H, 6.02; N, 4.65. Found: C, 43.68; H, 6.20; N, 4.50.

Compound **7b**: mp 103–105 °C. FAB-MS *m*/*z* (%): 439 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.21 (d, $J = 6.3$ Hz, 6H), 1.89 (t, $J = 5.2$ Hz, 2H), 3.77 (m, $J = 1.8$ Hz, 2H), 4.00 (d, $J = 3.0$ Hz, 4H), 4.60 (m, $J = 6.0$ Hz, 2H), 4.69 (t, $J = 5.2$ Hz, 2H), 8.02 (s, 2H). ^{13}C NMR ($CDCl_3$, δ): 15.72, 42.49, 56.19, 69.77, 71.68, 91.33, 125.60, 171.00. $[\alpha]_D^{20}$ −40.1 (*c* 2.0, MeOH). Anal. calcd for $C_{15}H_{20}F_6N_2O_6$: C, 41.10; H, 4.60; N, 6.39. Found: C, 41.30; H, 4.42; N, 6.25.

4.12. (2*S*,4*R*,5*R*)-2-(2,2-Dimethoxylethyl)-4-methyl-1,3-dioxan-5-yl-amine (6b) and *N*,*N*′-methylenebis[(2*S*,4*R*,5*R*)/(2*R*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisamine (8b)

(A) Using the same procedure as that for the preparation of **6a**, starting from 903 mg (3.0 mmol) of **5b**, 572 mg (93%) of **6b** was obtained as a colorless oil.
(B) Using the same procedure as that for the preparation of **6a**, starting from 439 mg (1.0 mmol) of **7b**, 221 mg (90%) of **8b** was obtained as a colorless oil.
(C) Using the same procedure as that for the preparation of **6a**, starting from 315 mg (3.0 mmol) of **3b**, 480 mg (78%) of **6b** and 80 mg (8%) of **8b** was obtained as a colorless oil.

Compound **6b**: FAB-MS *m*/*z* (%): 206 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.22 (d, $J = 6.1$ Hz, 3H), 1.87 (s, 2H), 1.89 (m, $J = 6.0$ Hz, 2H), 2.77 (m, $J = 1.9$ Hz, 1H), 3.25 (s, 3H), 3.25 (s, 3H), 4.00 (m, $J = 2.2$ Hz, 2H), 4.188 (t, $J = 6.0$ Hz, 1H), 4.21 (m, $J = 2.5$ Hz, 1H), 4.69 (t, $J = 5.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, δ): 18.68, 45.91, 48.11, 59.11, 76.39, 76.50, 93.35, 95.96. $[\alpha]_D^{20}$ −6.0 (*c* 2.0, $CHCl_3$). Anal. calcd for $C_9H_{19}NO_4$: C, 52.67; H, 9.33; N, 6.82. Found: C, 52.81; H, 9.50; N, 8.66.

Compound **8b**: FAB-MS *m*/*z* (%): 247 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.19 (d, $J = 6.5$ Hz, 6H), 1.72 (s, 4H), 1.95 (t, $J = 5.5$ Hz, 2H), 2.45 (d, $J = 1.5$ Hz, 2H), 3.85 (m, $J = 3.2$ Hz, 4H), 3.95 (d, $J = 1.5$ Hz, 1H), 3.97 (d, $J = 1.5$ Hz, 1H), 4.72 (t, $J = 5.5$ Hz, 2H). ^{13}C NMR ($CDCl_3$, δ): 17.61, 50.48, 58.94, 73.48, 75.15, 95.04. $[\alpha]_D^{20}$ −43.0 (*c* 2.0, MeOH). Anal. calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.37. Found: C, 53.79; H, 9.17; N, 11.25.

4.13. *N*-[(2*S*,4*R*,5*R*)-2-(2′,2′-Dimethoxyethyl)-4-methyl-1,3-dioxan-5-yl]benzoylamine (9b)

Using the same procedure as that for the preparation of **7a**, starting from 98 mg (0.48 mmol) of **6b**, 141 mg (95%) of the title compound was obtained as a colorless oil. FAB-MS *m*/*z* (%): 310 $[M+H]^+$. IR (KBr, cm^{-1}) *v*: 3441, 3052, 2970, 2933, 2866, 1655, 1601, 1571, 1480, 1410, 1376, 1360, 1175, 1065, 710, 692 cm^{-1}.^1H NMR ($CDCl_3$, δ): 1.21 (d, $J = 6.2$ Hz, 3H), 1.88 (m, $J = 6.2$ Hz, 2H), 3.24 (s, 3H), 3.25 (s, 3H), 3.78 (m, $J = 2.5$ Hz, 1H), 4.01 (m, $J = 2.4$ Hz, 2H), 4.18 (t, $J = 6.2$ Hz, 1H), 4.58 (m, $J = 2.7$ Hz, 1H), 4.68 (t, $J = 5.5$ Hz, 1H), 7.44 (t, $J = 9.3$ Hz, 2H), 7.52 (t, $J = 11.1$ Hz, 1H), 7.83 (d, $J = 11.1$ Hz, 2H), 8.00(s, 1H). In a NOESY experiment an NOE between the CH_3 at the 4-position and the CH_2 at the 2-position was observed. $[\alpha]_D^{20}$ −6.0 (*c* 2.0, $CHCl_3$). Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.01; H, 7.37; N, 4.64.

4.14. *N*,*N*′-Methylenebis[(2*S*,4*R*,5*R*)/(2*R*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisbenzoylamine (10b)

Using the same procedure as that for the preparation of **7a**, starting from 120 mg (0.48 mmol) of **8b**, 170 mg (76%) of the title compound was obtained as a colorless powder. Mp 134–137 °C. FAB-MS *m*/*z* (%): 247 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.19 (d, $J = 6.4$ Hz, 6H), 1.92 (t, $J = 5.6$ Hz, 2H), 3.66 (d, $J = 1.8$ Hz, 2H), 4.00 (d, $J = 3.8$ Hz, 4H), 4.53 (m, $J = 1.8$ Hz, 2H), 4.67(t, $J = 1.9$ Hz, 2H), 7.44 (t, $J = 9.1$ Hz, 4H), 7.52 (t, $J = 10.8$ Hz, 2H), 7.83 (d, $J = 10.8$ Hz, 2H), 7.89 (s, 1H). In a NOESY experiment, NOEs between the CH_3 at the 4-position and the CH_2 at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. $[\alpha]_D^{20}$ −35.1 (*c* 2.0, MeOH). Anal. calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 66.19; H, 6.71; N, 6.25.

4.15. *N*-[(2*S*,5*S*)-2-(2,2-Dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]trifluoroacetylamine (5c) and *N*-[(2*R*,5*S*)-2-(2,2-dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]trifluoroacetylamine (6c)

Using the same procedure as that for the preparation of **5a**, starting from 603 mg (3.0 mmol) of **4c**, 82 mg (13%) of **5c** and 83 mg (13%) of **6c** were obtained as a colorless powder.

Compound **5c**: mp 120–122 °C. FAB-MS *m*/*z* (%): 302 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.46 (m, $J = 5.0$ Hz, 2H), 1.67 (t, $J = 5.0$ Hz, 2H), 1.90 (t, $J = 4.8$ Hz, 2H), 3.23 (s, 6H), 3.37 (t, $J = 4.5$ Hz, 2H), 4.18 (t, $J = 5.0$ Hz, 1H), 4.18 (t, $J = 4.5$ Hz, 1H), 4.91 (t, $J = 5.1$ Hz, 1H), 8.00 (s, 1H). In a NOE experiment, a positive NOE between the NH at the 5-position and the CH_2 at the 2-position was observed. ^{13}C NMR ($CDCl_3$, δ): 22.00, 33.16, 41.90, 48.10, 48.20, 63.80, 71.38, 86.27, 96.37, 125.59, 170.60. $[\alpha]_D^{20}$ −33.4 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_{11}H_{18}F_3NO_5$: C, 43.86; H, 6.02; N, 4.65. Found: C, 43.69; H, 5.90; N, 4.79.

Compound **6c**: mp 107–109 °C. FAB-MS *m*/*z* (%): 302 $[M+H]^+$. ^1H NMR ($CDCl_3$, δ): 1.46 (m, $J = 4.2$ Hz, 2H), 1.65 (q, $J = 4.0$ Hz, 2H), 1.88 (t, $J = 4.6$ Hz, 2H), 3.25 (s, 6H), 3.36 (t, $J = 4.2$ Hz, 2H), 4.20 (d, $J = 5.0$ Hz, 1H), 4.23 (d, $J = 4.9$ Hz, 1H), 4.95 (t, $J = 4.0$ Hz, 1H), 8.00 (s, 1H). In a NOESY experiment,

no NOE was observed. ^{13}C NMR ($CDCl_3$, δ): 21.89, 33.09, 41.88, 47.98, 48.00, 63.66, 71.38, 86.27, 96.41, 125.58, 170.77. $[\alpha]_D^{20}$ −22.5 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_{11}H_{18}F_3NO_5$: C, 43.86; H, 6.02; N, 4.65. Found: C, 44.05; H, 6.20; N, 4.54.

4.16. *N*-[(2*S*,5*S*)-2-(2,2-Dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]amine (7c) and *N*-[(2*R*,5*S*)-2-(2,2-dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]amine (8c)

(A) Using the same procedure as that for the preparation of **6a**, starting from 315 mg (3.0 mmol) of **3c**, 480 mg (31%) of **7c** and 80 mg (15%) of **8c** were obtained as a colorless oil.
(B) Using the same procedure as that for preparation of **6a**, starting from 602 mg (2.0 mmol) of **5c**, 373 mg (91%) of **7c** was obtained as a colorless oil.
(C) Using the same procedure as that for preparation of **6a**, starting from 602 mg (2.0 mmol) of **6c**, 381 mg (93%) of **8c** was obtained as a colorless oil.

Compound **7c**: FAB-MS *m*/*z* (%): 206 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, δ): 1.66 (q, J = 4.2 Hz, 2H), 1.90 (t, J = 4.8 Hz, 2H), 2.00 (s, 2H), 2.99 (m, J = 4.5 Hz, 1H), 3.35 (s, 6H), 3.40 (t, J = 5.1 Hz, 2H), 3.62 (d, J = 6.0 Hz, 2H), 4.20 (t, J = 5.8 Hz, 1H). In a NOESY experiment, a NOE between the NH at the 5-position and the CH_2 at the 2-position was observed. ^{13}C NMR ($CDCl_3$, δ): 35.88, 41.99, 47.85, 48.11, 48.20, 58.66, 72.47, 91.36. $[\alpha]_D^{20}$ −38.1 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_9H_{19}NO_4$: C, 52.67; H, 9.33; N, 6.28. Found: C, 52.53; H, 9.25; N, 6.41.

Compound **8c**: FAB-MS *m*/*z* (%): 206 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, δ): 1.65 (q, J = 4.0 Hz, 2H), 1.88 (t, J = 4.6 Hz, 2H), 2.00 (s, 2H), 2.94 (m, J = 4.7 Hz, 1H), 3.34 (s, 6H), 3.39 (t, J = 5.2 Hz, 2H), 3.56 (d, J = 6.2 Hz, 2H), 4.33 (t, J = 6.0 Hz, 1H). In a NOESY experiment, no NOE was observed. ^{13}C NMR ($CDCl_3$, δ): 35.75, 41.87, 47.70, 48.00, 48.11, 58.57, 72.22, 91.01. $[\alpha]_D^{20}$ 30.2 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_9H_{19}NO_4$: C, 52.67; H, 9.33; N, 6.28. Found: C, 52.82; H, 9.49; N, 6.16.

4.17. *N*-[(2*S*,5*S*)-2-(2,2-Dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]benzoylamine (9c)

Using the same procedure as that for the preparation of **7a**, starting from 205 mg (1.00 mmol) of **7c**, 253 mg (82%) of the title compound was obtained as a colorless powder. Mp 67–69 °C. FAB-MS *m*/*z* (%): 310 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, δ): 1.90 (m, J = 4.8 Hz, 2H), 1.96 (t, J = 3.3 Hz, 2H), 3.35 (s, 6H), 3.64 (dd, J = 6.9 Hz, J = 5.1 Hz, 2H), 3.92 (d, J = 7.2 Hz, 1H), 4.04 (d, J = 7.2 Hz, 1H), 4.34 (m, J = 4.0 Hz, 1H), 4.53 (t, J = 3.6 Hz, 1H), 4.89 (t, J = 3.6 Hz, 1H), 7.45 (t, J = 5.2 Hz, 2H), 7.52 (d, J = 4.5 Hz, 1H), 7.79 (d, J = 4.5 Hz, 2H), 7.99 (s, 1H). In a NOESY experiment, a NOE between the NH at the 5-position and the CH_2 at the 2-position was observed. ^{13}C NMR ($CDCl_3$, δ): 21.90, 33.10, 41.89, 47.98, 48.02, 63.69, 71.79, 86.31, 96.39, 127.30, 128.55, 132.00, 133.48, 167.85. $[\alpha]_D^{20}$ 13.0 (*c* 0.02, $CHCl_3$). Anal. calcd for $C_{16}H_{23}F_3NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.10; H, 7.45; N, 4.51.

4.18. *N*-[(2*R*,5*S*)-2-(2,2-Dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]benzoylamine (10c)

Using the same procedure as that for the preparation of **7a**, starting from 205 mg (1.00 mmol) of **8c**, 247 mg (80%) of the title compound was obtained as a colorless powder. Mp 85–87 °C. FAB-MS *m*/*z* (%): 310 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, δ): 1.91 (m, J = 4.9 Hz, 2H), 1.97 (t, J = 3.4 Hz, 2H), 3.35 (s, 6H), 3.64 (dd, J = 6.6 Hz, J = 5.0 Hz, 2H), 3.92 (d, J = 7.0 Hz, 1H), 4.04 (d, J = 7.0 Hz, 1H), 4.34 (m, J = 4.1 Hz, 1H), 4.53 (t, J = 3.5 Hz, 1H), 4.91 (t, J = 3.8 Hz, 1H), 7.45 (t, J = 5.4 Hz, 2H), 7.52 (d, J = 4.6 Hz, 1H), 7.79 (d, J = 4.6 Hz, 2H), 8.00 (s, 1H). In a NOESY experiment, no NOE between the NH at the 5-position and the CH_2 at the 2-position was observed. ^{13}C NMR ($CDCl_3$, δ): 21.93, 33.13, 42.00, 47.99, 48.02, 63.69, 71.77, 86.38, 96.40, 127.31, 128.56, 132.02, 133.49, 167.87. $[\alpha]_D^{20}$ 15.7 (*c* 0.02, $CHCl_3$). Anal. calcd for $C_{16}H_{23}F_3NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.22; H, 7.61; N, 4.72.

4.19. Animals

Male Kunming mice (about 25 g) were inbred and grown in the animal room at the College of Pharmacy, Peking University. The animal room was maintained at 23 ± 2 °C with a 12 h light/dark cycle. Food and tap water were supplied ad libitum. The ethical guidelines described in the NIH Guide for Care and Use of Laboratory Animals were followed throughout the experiments.

4.20. Xylene-induced ear edema[15,16]

Male Kunming mice were randomly divided into three groups of 12 mice, namely the test group, vehicle control group and positive control group. The mice in vehicle control group were administered orally a suspension of aspirin in CMC at a dosage of 20 mg/kg, and a concentration of 0.3 mg/ml, while the mice in the test group were administered orally a suspension of 1,3-dioxacycloalkane in CMC at a dosage of 20, 4.0, and 0.8 mg/kg, and a concentration of 2.0, 0.4, and 0.08 mg/ml. Thirty minutes later, 0.03 ml of xylene was applied to both the anterior and posterior surfaces of the right ear. The left ear was considered as control. Two hours after xylene application, the mice were killed and both ears were removed. Using a cork borer with a diameter of 7 mm, several circular sections were taken and weighed. The increase in weight caused by the irritant was measured through subtracting the weight of the untreated left ear section from that of the treated right ear section. The statistical analysis of the data was carried out by use of ANOVA, $p < 0.05$ considered significant.

Acknowledgments

S.P. wishes to thank National Key-Basic Project of China (2003CCA04400), National Natural Science Foundation of China (20232020 and 30372433), and

Scientific Foundation Guangzhou City of China for financial support. Work performed in LLNL is carried out under the auspices of the U.S. Department of Energy by the University of California under contract W-7405-Eng-48.

References and notes

1. (a) Kuchera, S.; Barth, H.; Jacobson, P.; Metz, A.; Schaechtele, C.; Schrier, D. *Agents Actions* **1993**, *39*, 169; (b) Basu, A. *Pharmacol. Ther.* **1993**, *59*, 257.
2. Amon, U.; Dietz, K. R. *Arch. Dermatol. Res.* **1992**, *284*, 8.
3. Fisher, G. J.; Tavakkol, A.; Leach, K. *J. Invest. Dermatol.* **1993**, *101*, 553.
4. Rasmussen, H. H.; Celis, J. E. *J. Invest. Dermatol.* **1993**, *101*, 560.
5. Goekjian, P. G.; Jirousek, M. R. *Curr. Med. Chem.* **1999**, *6*, 877.
6. Reynolds, N. J. *Arch. Dermatol. Res.* **1997**, *289*, 520.
7. (a) Stanley, P. L.; Steiner, S.; Havens, M.; Tramposch, K. M. *Skin Pharmacol.* **1991**, *4*, 262; (b) Scott, M.; Jayasree, V.; Roshantha, A. S. *J. Med. Chem.* **2001**, *44*, 281.
8. (a) Tamamura, H.; Sigano, D. M.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **2004**, *47*, 644; (b) Nacro, K.; Bienfait, B.; Lee, J.; Han, K.; Kang, J.; Benzaria, S.; Lewin, N. E.; Bhattacharyya, D. K.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **2000**, *43*, 921; (c) Lee, J.; Han, K.-C.; Kang, J.-H.; Pearce, L. L.; Lewin, N. E.; Yan, S.; Benzaria, S.; Nicklaus, M. C.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **2003**, *46*, 2794; (d) Pettit, G. R.; Ducki, S.; Tan, R.; Gardella, R. S.; McMahon, J. B.; Boyd, M. R.; Pettit, G. R.; Blumberg, P. M.; Lewin, N. E.; Doubek, D. L.; Tackett, L. P.; Williams, M. D. *J. Nat. Prod.* **2002**, *65*, 1262; (e) Kang, J.-H.; Siddiqui, M. A.; Sigano, D. M.; Krajewski, K.; Lewin, N. E.; Pu, Y.; Blumberg, P. M.; Lee, J.; Marquez, V. E. *Org. Lett.* **2004**, *6*, 2413.
9. Jiang, J. B.; Johnson, M. G.; Nichols, J. U.S. Patent 5,360,818, 1994.;
10. (a) Shi, R. X.; Ong, C. N.; Shen, H. M. *Cancer Res.* **2005**, *65*, 7815; (b) Pan, Q.; Bao, L. W.; Kleer, C. G.; Sable, M. S.; Griffith, K. A.; Teknos, T. N.; Merajver, S. D. *Cancer Res.* **2005**, *65*, 8366.
11. Aksoy, E.; Goldman, M.; Willems, F. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 183.
12. (a) Hanlon, P. R.; Fy, P.; Wright, G. L.; Steenbergen, C.; Arcasoy, M. O.; Murphy, E. *FASEB J.* **2005**, *19*, 1323; (b) Churchill, E. N.; Murrile, C. L.; Chen, C. L.; Mochly-Rosen, D.; Szweda, L. I. *Circ. Res.* **2005**, *97*, 78.
13. Bi, L.; Zhao, M.; Wang, C.; Peng, S. *Eur. J. Org. Chem.* **2000**, *2669*.
14. Bi, L.; Zhao, M.; Wang, C.; Peng, S.; Winterfeldt, E. *J. Org. Chem.* **2002**, *67*, 22.
15. Bi, L.; Zhang, Y.; Zhao, M.; Wang, C.; Chan, P.; Tok, J. B.-H.; Peng, S. *Bioorg. Med. Chem.* **2005**, *13*, 5640.
16. Romay, C.; Armesto, J.; Remirez, D.; Gonzalez, R.; Ledon, N.; Garcia, I. *Inflamm. Res.* **1998**, *47*, 334.
17. Smith, A. B.; Cho, Y. S.; Zawacki, L. E.; Hirschmann, R.; Pettit, G. R. *Org. Lett.* **2001**, *3*, 4063.