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# Rapid novel divergent synthesis and muscarinic agonist profile of all four optical isomers of *N*,*N*,*N*-trimethyl(6-methyl-1,4-dioxan-2-yl)methanaminium iodide

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**Abstract**—Two stereoselective parallel divergent four-step procedures to obtain all four enantiomeric forms of *N*,*N*,*N*-trimethyl(6-methyl-1,4-dioxan-2-yl)methanaminium iodide were developed. Enantiomeric purity was determined by quantitative $^1$H NMR spectroscopy in the presence of the chiral shift reagent (+)-MTPA. The biological profile of the obtained compounds was evaluated at all muscarinic receptor subtypes by binding and functional assays.


In recent years the study of muscarinic agonists has acquired a growing importance, due to the numerous therapeutic opportunities potentially offered by the activation of the corresponding receptors.[1]

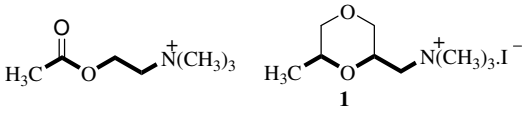
On the basis of genetic[2] and pharmacological characterizations,[3] muscarinic receptors have been subdivided into five subtypes ($M_1$–$M_5$).[4] They mediate the metabotropic actions of acetylcholine in the nervous system by coupling to heterotrimeric guanine nucleotide binding proteins and subsequently mobilizing second messenger systems.[4] A growing body of data indicates that they also mediate autocrine functions of acetylcholine.[5]

The clinical use of muscarinic agonists and antagonists is limited by various side effects in both the peripheral and central nervous system, due to the lack of a marked subtype-discrimination. At present, antagonists relatively selective for some subtypes are known, while despite significant effort, the identification of subtype selective agonists has met with only modest success.

Chirality is a key factor in the efficacy of many drug products and an essential feature of the molecular structure of biologically active asymmetric compounds. In fact, opposite absolute configurations at pharmacophoric groups are frequently responsible for differences in the biological response, mainly in terms of potency and receptor subtype selectivity.[6] Design, development, and marketing of new chiral active substances are now major themes in drug research.[7]

It is well known that muscarinic receptors display stereoselective requirements and the biological activity of muscarinic ligands is closely related to their stereochemistry.[8] For this reason, we recently synthesized and studied the *cis* and *trans* diastereoisomers of *N*,*N*,*N*-trimethyl(6-methyl-1,4-dioxan-2-yl)methanaminium iodide (**1**),[9] a conformationally constrained model of the endogenous ligand acetylcholine (Fig. 1).

Though the *cis* diastereoisomer (±)-**1a** proved to be particularly active and more potent than the *trans* structure



**1**

**Figure 1.** Compound **1** is a conformationally constrained model of the endogenous ligand acetylcholine.

*Keywords*: Muscarinic receptors; Muscarinic agonists; 1,4-Dioxane nucleus; Subtype selectivity; Receptor enantioselectivity; Stereoselective synthesis.
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(±)-**1b**, this latter displayed an interesting selectivity toward the cardiac muscarinic subtype with respect to the other subtypes.[9] In the attempt to obtain the four enantiomers, we previously followed two parallel stereoselective routes,[9] according to what had been reported for compounds bearing 1,4-dioxane nucleus.[10] Unfortunately, only the *cis* enantiomeric forms were obtained. Therefore, in the present paper we describe two parallel novel divergent four-step stereoselective synthetic sequences, which have been carried out to give the two pairs of diastereoisomers, and the biological profile of the obtained compounds at all muscarinic receptor subtypes by binding and functional assays.

The two pairs of enantiomers of (±)-**1a** and (±)-**1b** were prepared by stereoselective synthesis, according to the parallel reaction sequences reported in Scheme 1. The preparation of (*S*)-1-(allyloxy)propan-2-ol [(+)-(*S*)-**2**], previously synthesized in three steps,[11] was readily accomplished starting from the commercially available (−)-(*S*)-2-methyloxirane. The intermediate alcohol was subjected to oxymercuration-reduction reaction with mercury(II) acetate followed by an aqueous solution of iodine and potassium iodide, which afforded a mixture of the diastereoisomeric forms (2*S*,6*S*)- and (2*R*,6*S*)-2-(iodomethyl)-6-methyl-1,4-dioxane [(2*S*,6*S*)/(2*R*,6*S*)-**3**]. The amination of (2*S*,6*S*)/(2*R*,6*S*)-**3** with dimethylamine gave the corresponding mixture of amines, whose diastereoisomers (+)-(2*R*,6*S*)-**4a** and (+)-(2*S*,6*S*)-**4b** were separated by column chromatography. Finally the two methiodides (+)-(2*R*,6*S*)-**1a** and (+)-(2*S*,6*S*)-**1b** were prepared by treating an ethereal solution of the corresponding amines with methyl iodide.

The corresponding diastereoisomers (−)-(2*S*,6*R*)-**1a** and (−)-(2*R*,6*R*)-**1b** were synthesized with the same procedure as described for (+)-(2*R*,6*S*)-**1a** and (+)-(2*S*,6*S*)-**1b**, starting from (+)-(*R*)-2-methyloxirane [(−)-(*R*)-**2**] (Scheme 1).

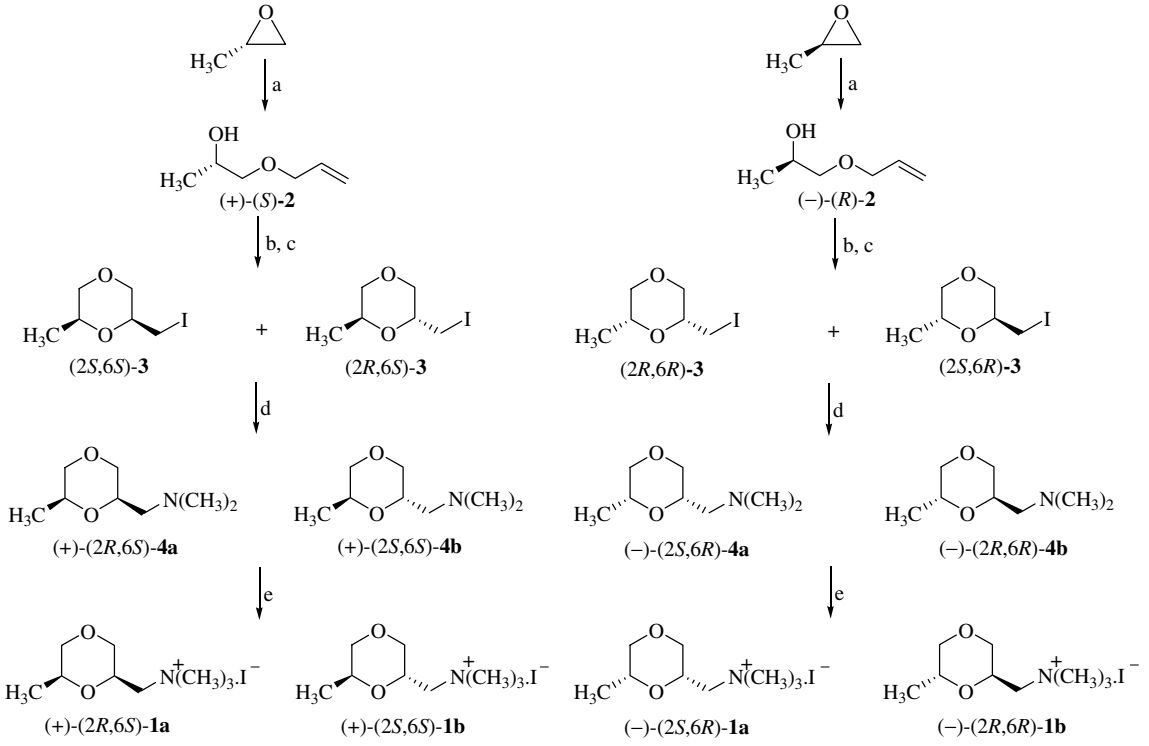
The final *trans* enantiomeric methiodides (−)-(2*S*,6*S*)-**1b** and (+)-(2*R*,6*R*)-**1b** were obtained in moderate yields but in an amount sufficient to allow their biological profile at all muscarinic receptor subtypes to be determined.

Moreover, though the overall yields for the *cis* enantiomeric methiodides (−)-(2*S*,6*R*)-**1a** and (+)-(2*R*,6*S*)-**1a** were similar to those obtained by the previous synthetic routes,[9] the preparation time was markedly shortened since the synthetic steps were reduced from eight to four.

Experimental details and data for these synthetic procedures are cited in References and notes.[12–16]

The stereochemical relationship between the 2-side chain and the 6-methyl group of the diastereoisomers was assigned comparing the $^1$H NMR spectra of enantiomeric amines with those of the corresponding racemic mixtures (±)-**1a** and (±)-**1b**, whose structure had been previously determined by single-crystal X-ray diffraction analysis.[9]

Enantiomeric purity of amines (+)-(2*R*,6*S*)-**1a**, (−)-(2*S*,6*R*)-**1a**, (+)-(2*S*,6*S*)-**1b**, and (−)-(2*R*,6*R*)-**1b**, determined by $^1$H NMR spectroscopy in comparison with the spectra of racemic compounds (±)-**1a** and (±)-**1b**, and on addition of the chiral shift reagent (+)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid




**Scheme 1.** Reagents: (a) $CH_2$=$CHCH_2OH$, Na; (b) $(CH_3COO)_2Hg$, $H_2O$; (c) KI, $I_2$; (d) $Me_2NH$, benzene; (e) $CH_3I$, diethyl ether.

[(+)-(*R*)-MTPA],[17] was found to be >98% (detection limit) for all the enantiomers. The spectral data for (+)-(2*R*,6*S*)-**1a** and (−)-(2*S*,6*R*)-**1a** in the presence of (+)-(*R*)-MTPA were identical to those previously reported.[9] Analogously, in the case of *trans* enantiomeric forms the $^1$H NMR spectrum of racemic (±)-**1b** showed a double doublet at $\delta$ 1.12 ppm for the 6-methyl protons, whereas only one doublet was observed for (+)-(2*S*,6*S*)-**1b** and (−)-(2*R*,6*R*)-**1b** at $\delta$ 1.05 ppm and $\delta$ 1.12 ppm, respectively.

The pharmacological profile of all methiodides was evaluated by receptor binding assays following a protocol previously described.[18] Acetylcholine and carbachol were used as reference compounds. $^3$[H] NMS was the radioligand used to label cloned human muscarinic hm1–hm5 receptors expressed in Chinese hamster ovary cells (CHO). Affinity values, expressed as p$K_i$, are reported in Table 1.

Moreover, the muscarinic activity of the new compounds (+)-(2*S*,6*S*)-**1b** and (−)-(2*R*,6*R*)-**1b** was also evaluated by functional studies performed on guinea-pig stimulated left atria ($M_2$), ileum ($M_3$), and lung strips ($M_4$) following a protocol already described in detail.[18] Potency values, expressed as p$D_2$, are reported in Table 2 along with those of (±)-**1a**, (+)-(2*R*,6*S*)-**1a**, (−)-(2*S*,6*R*)-**1a**, (±)-**1b**, (±)-muscarine, and carbachol, which were included for useful considerations on structure– and stereochemistry–activity relationships.

From an analysis of binding data it is possible to observe that, analogously to carbachol and acetylcholine, all tested compounds show the highest affinity for the hm2 subtype. The $M_2$ selectivity profile of acetylcholine has been explained by entropic factors, which make the interaction with $M_2$ subtype more favorable than those with $M_1$ and $M_5$ subtypes.[19] Moreover, also some other cyclic ligands, such as muscarine,[20] have been reported to be $M_2$-selective in binding assays. Therefore, since all compounds of the present study are structurally related to acetylcholine and muscarine, their $M_2$ selectivity profile is not surprising and might confirm what has previously been reported.

Another interesting observation is that affinity and selectivity for hm1–hm5 receptor subtypes depends on the stereochemistry (Table 1). In fact, the stereochemical relationship between the 6-methyl group and the 2-side chain of *N*,*N*,*N*-trimethyl(6-methyl-1,4-dioxan-2-yl) methanaminium iodide plays an important role in drug-receptor affinity, the *cis* racemic compound (±)-**1a** showing affinity values higher than those of the *trans* (±)-**1b** at all five receptor subtypes. A similar behavior is observed by comparing the p$D_2$ values of the two racemic com-

**Table 1.** Affinity constants, expressed as p$K_i$,[a] (−log $K_i$) of compounds (±)-**1a**, (±)-**1b**, their corresponding enantiomers, carbachol, and acetylcholine for human cloned muscarinic receptors, expressed in CHO cells

| Compound | p$K_i$[a] | | | | |
|---|---|---|---|---|---|
| | hm1 | hm2 | hm3 | hm4 | hm5 |
| (±)-**1a** | 4.52 (4.46–4.61) | 5.68 (5.58–5.76) | 5.12 (5.00–5.23) | 4.94 (4.86–5.06) | 5.11 (5.04–5.17) |
| (+)-(2*R*,6*S*)-**1a** | 4.89 (4.85–4.92) | 5.90 (5.81–5.99) | 5.47 (5.36–5.57) | 5.01 (4.91–5.12) | 5.34 (5.27–5.40) |
| (−)-(2*S*,6*R*)-**1a** | <4 | 5.16 (5.07–5.50) | 4.44 (4.35–4.55) | 4.16 (4.09–4.24) | 4.35 (4.29–4.42) |
| (±)-**1b** | <4 | 5.31 (5.22–5.42) | 4.45 (4.38–4.54) | 4.06 (3.99–4.12) | 4.17 (4.10–4.24) |
| (+)-(2*S*,6*S*)-**1b** | 4.13 (4.06–4.17) | 5.28 (5.20–5.15) | 4.63 (4.52–4.73) | 4.34 (4.27–4.43) | 4.52 (4.45–4.59) |
| (−)-(2*R*,6*R*)-**1b** | <4 | 4.21 (4.12–4.32) | 4.21 (4.12–4.32) | <4 | 4.06 (4.00–4.14) |
| Carbachol | 4.42 (4.36–4.51) | 5.91 (5.86–5.97) | 4.36 (4.27–4.46) | 5.20 (5.12–5.27) | 4.16 (4.01–4.24) |
| Acetylcholine | 4.87 (4.84–4.90) | 6.80 (6.74–6.86) | 5.15 (5.08–5.24) | 5.07 (5.01–5.14) | 5.01 (4.99–5.04) |

[a] The values represent the geometric means of three to six independent experiments. Ranges are given in parentheses.

**Table 2.** Potency values, expressed as −log $ED_{50}$ (p$D_2$), intrinsic activity ($\alpha$),[a] and dissociation constant (p$K_b$)[b] of compounds (±)-**1a**, (±)-**1b**, their corresponding enantiomers, carbachol, and (±)-muscarine at $M_1$–$M_4$ muscarinic receptor subtypes[c]

| Compound | Rabbit vas deferens ($M_1$) | | Guinea pig atrium ($M_2$) | | Guinea pig ileum ($M_3$) | | Guinea pig lung ($M_4$) | |
|---|---|---|---|---|---|---|---|---|
| | $\alpha$ | p$D_2$ (p$K_b$) | $\alpha$ | p$D_2$ (p$K_b$) | $\alpha$ | p$D_2$ (p$K_b$) | $\alpha$ | p$D_2$ (p$K_b$) |
| (±)-**1a** | 1 | 5.65 ± 0.06 | 1 | 7.57 ± 0.11 | 1 | 7.34 ± 0.13 | 0.81 ± 0.07 | 5.90 ± 0.14 |
| (+)-(2*R*,6*S*)-**1a** | 1 | 6.78 ± 0.04 | 1 | 6.80 ± 0.10 | 1 | 7.65 ± 0.12 | 1 | 5.87 ± 0.15 |
| (−)-(2*S*,6*R*)-**1a** | | (<5)[e] | 1 | 7.35 ± 0.21 | 1 | 6.53 ± 0.16 | 0.75 ± 0.11 | 4.34 ± 0.20 |
| (±)-**1b** | 1 | 5.08 ± 0.24 | 1 | 6.66 ± 0.19 | 1 | 6.02 ± 0.16 | 0.53 ± 0.07 | 6.01 ± 0.03 |
| (+)-(2*S*,6*S*)-**1b** | | [d] | 0.90 ± 0.01 | 6.18 ± 0.18 | 1 | 6.26 ± 0.10 | 0.77 ± 0.02 | 5.79 ± 0.11 |
| (−)-(2*R*,6*R*)-**1b** | | [d] | 0.62 ± 0.02 | 5.27 ± 0.06 | 1 | 4.54 ± 0.08 | 0.42 ± 0.02 | 5.22 ± 0.02 |
| Carbachol | | [d] | 1 | 7.33 ± 0.08 | 1 | 6.68 ± 0.01 | 1 | 5.43 ± 0.03 |
| (±)-Muscarine | | [d] | 1 | 6.72 ± 0.09 | 1 | 7.29 ± 0.07 | | [d] |

[a] Intrinsic activity was measured by the ratio between the maximum response of the agonist and the maximum response of McN-A-343 at $M_1$, and arecaidine propargyl ester (APE) at $M_2$, $M_3$, and $M_4$ subtypes.
[b] Dissociation constants were calculated from the equation: log(DR − 1) = log[ant] − log $K_b$ according to van Rossum.[22]
[c] The results are means (±SEM) of four to six independent experiments.
[d] Not determined.
[e] This compound showed no agonist activity and, when tested as antagonist, proved inactive up to 10 μM.

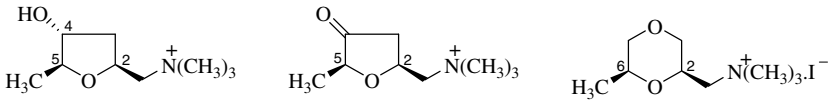



**Figure 2.** Stereochemistry of muscarine, (−)-(2*S*,5*S*)-muscarone, and (+)-(2*R*,6*S*)-**1a**.

pounds (Table 2). Concerning the stereoselectivity the eutomers are (+)-(2*R*,6*S*)-**1a** and (+)-(2*S*,6*S*)-**1b**, which share the same absolute configuration at position 6. This may indicate that of the two stereogenic centers the one at position 6 seems stereochemically more important than that at position 2 for drug-receptor recognition. Moreover, since the absolute configuration of (+)-(2*R*,6*S*)-**1a**, which shows the highest affinities, is consistent with those of muscarine[20] and some muscarine pentatomic cyclic analogues, such as muscarone[21] (Fig. 2), we can hypothesize that all these compounds interact with the same receptor binding sites of the five muscarinic receptor subtypes in a similar fashion.

The interesting behavior of the two *cis* enantiomeric forms at $M_2$ and $M_3$ receptor subtypes observed in functional studies and previously discussed[9] is not confirmed by binding studies, where both enantiomers show the same affinity profile (hm2 > hm3 > hm5 > hm4 > hm1).

Probably, the differences between binding and functional data can be explained on the basis that $pK_i$ values exclusively express the ability to bind to the receptor binding site without providing any information on pharmacological parameters, such as efficacy, whereas $pD_2$ values indicate the ability to activate the receptor. Therefore, the functional selectivity might be ascribed to a difference in receptor activation efficacy.

Moreover, from functional studies it can be observed that, though between the two *trans* enantiomeric forms the eutomer is (+)-(2*S*,6*S*)-**1b**, the selectivity for $M_2$ subtype shown by the racemic compound (±)-**1b** seems to reside in the 2*R*,6*R* form. In fact, compound (−)-(2*R*,6*R*)-**1b**, though with $pD_2$ values lower than those of its corresponding enantiomer, maintains the interesting $M_2/M_3$ selectivity ratio as the racemic compound (±)-**1b**.

In conclusion, we have developed two practical and parallel divergent four-step synthetic routes for the preparation of all enantiomers of *N*,*N*,*N*-trimethyl(6-methyl-1,4-dioxan-2-yl)methanaminium iodide. These procedures have allowed us to reduce the preparation time of *cis* enantiomeric forms with overall yields similar to those previously reported and, above all, to obtain the *trans* enantiomeric forms. Moreover, the new stereoselective method represents a convenient access to the rapid synthesis of 2,6-disubstituted enantiomeric dioxane compounds acting as useful tools for muscarinic receptor subtype characterization.

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12. *Synthesis of (+)-(S)-1-(allyloxy)propan-2-ol [(+)-(S)-**2**]:* (−)-(*S*)-2-Methyloxirane (10.0 g, 0.17 mol) was added dropwise to a stirred solution of freshly cut sodium (1.2 g, 0.05 mol) in allyl alcohol (110 ml) at rt. After 1 h at rt the reaction mixture was refluxed for 4 h. Most of the unreacted allyl alcohol was then separated by distillation at atmospheric pressure. After cooling to rt 6 N aqueous sulfuric acid (10 ml) was added to the residual solution to neutralize the sodium alloxide, and solvent removal was continued to afford a residual oil: 8.60 g (44% yield); 45 °C/20 mm Hg; $[\alpha]_{20}^{D}$ +20.50 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.18 (d, 3, $CH_3$), 2.48 (br s, 1 OH) 3.22 (dd, 1, $CH_2O$), 3.41 (dd, 1, $CH_2O$), 3.91 (m, 1, CHO) 4.01 (m, 2, $CH_2$), 5.09–5.98 (m, 3, CH=$CH_2$). The $^1$H NMR spectrum was similar to that reported for the corresponding racemic form.[13] (−)-(*R*)-1-(Allyloxy)propan-2-ol [(−)-(*R*)-**2**] was prepared as described for (+)-(*S*)-**2** starting from (+)-(*R*)-2-methyloxirane (10.0 g, 0.17 mol) to afford an oil: 8.75 g (44% yield); 45 °C/20 mm Hg; $[\alpha]_{20}^{D}$ −20.20 (*c* 1, $CHCl_3$). The $^1$H NMR spectrum was identical to that of (+)-(*S*)-**2**.
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14. *Synthesis of (2S,6S)/(2R,6S)-2-(iodomethyl)-6-methyl-1,4-dioxane [(2S,6S)/(2R,6S)-**3**]:* A solution of mercury(II) acetate (20.1 g, 0.06 mol) in $H_2O$ (75 ml) and acetic acid (0.1 ml) was added to a stirred solution of (+)-(*S*)-**2** (7.0 g, 0.06 mol). The reaction mixture was heated to reflux for 45 min, then allowed to stand overnight at rt. After filtering the reaction mixture a solution of KI (10.3 g, 0.06 mol) in $H_2O$ (34 ml) was added to the filtrate and (6*S*)-((6-methyl-1,4-dioxan-2-yl)methyl)mercury(II) iodide separated as an oil, which was dissolved in $CHCl_3$ (66 ml). A solution of $I_2$ (12.2 g, 0.05 mol) in $CHCl_3$ was added and the reaction mixture was heated to boiling and then allowed to stand at rt for 18 h. The organic phase was washed with 10% $Na_2SO_3$, 10% KI, and dried over $Na_2SO_4$. The evaporation of the solvent in vacuo afforded

a residue, which was purified by column chromatography, eluting with cyclohexane–EtOAc 98:2 to afford a mixture of the two diastereoisomers [(2*S*6*S*)/(2*R*,6*S*)-**3**] (ratio 75:25) as an oil: 5.9 g (41% yield); $^1$H NMR ($CDCl_3$) $\delta$ 1.12 and 1.17 (two d, 6, $CH_3$), 3.00–4.02 (m, 16H, cycle, $CH_2I$). (2*R*,6*R*)/(2*S*,6*R*)-2-(Iodomethyl)-6-methyl-1,4-dioxane [(2*R*,6*R*)/(2*S*,6*R*)-**3**] was prepared as described for (2*S*,6*S*)/(2*R*,6*S*)-**3** starting from (−)-(*R*)-**2** (7.0 g, 0.06 mol). A mixture of the two diastereoisomers [(2*R*,6*R*)/(2*S*,6*R*)-**3**] (ratio 75:25) was obtained as an oil: 5.8 g (40% yield). The $^1$H NMR spectrum was comparable to that of (2*S*,6*S*)/(2*R*,6*S*)-**3**.

15. *Synthesis of (+)-(2R,6S)-N,N-dimethyl(6-methyl-1,4-dioxan-2-yl)methanamine, (+)-(2S,6S)-N,N-dimethyl (6-methyl-1,4-dioxan-2-yl)methanamine, (−)-(2S,6R)-N,N-dimethyl(6-methyl-1,4-dioxan-2-yl)methanamine, and (−)-(2R,6R)-N,N-dimethyl(6-methyl-1,4-dioxan-2-yl) methanamine [(+)-(2R,6S)-***4a***, *(+)-(2S,6S)-***4b**, *(−)-(2S,6R)-***4a**, *and (−)-(2R,6R)-***4b***]:* These amines were prepared following the procedure described in Ref. 9 . The mixture of diastereoisomers (+)-(2*R*,6*S*)-**4a** and (+)-(2*S*,6*S*)-**4b** was separated by column chromatography eluting with petroleum ether/EtOAc/$CH_3OH$/$NH_4OH$ (8:3:1:0.02). The *cis* isomer (+)-(2*R*,6*S*)-**4a** eluted first: 1.6 g (55% yield); $[\alpha]_{20}^{D}$ +12.45 (*c* 1, $CHCl_3$). The $^1$H NMR spectrum was comparable to that previously reported.[9] The second fraction was the *trans* isomer (+)-(2*S*,6*S*)-**4b**: 0.32 g (11% yield); $[\alpha]_{20}^{D}$ +4.15 (*c* 1, $CHCl_3$). The $^1$H NMR spectrum was comparable to that previously reported for the corresponding racemic form.[9] The mixture of diastereoisomers (−)-(2*S*,6*R*)-**4a** and (−)-(2*R*,6*R*)-**4b** was separated as described for (+)-(2*R*,6*S*)-**4a** and (+)-(2*S*,6*S*)-**4b**. The *cis* isomer (−)-(2*S*,6*R*)-**4a** eluted first: 1.7 g (53% yield); $[\alpha]_{20}^{D}$ −12.55 (*c* 1, $CHCl_3$). The $^1$H NMR spectrum was comparable to that previously reported.[9] The second fraction was the *trans* isomer (−)-(2*R*,6*R*)-**4b**: 0.38 g (12% yield); $[\alpha]_{20}^{D}$ −4.06 (*c* 1, $CHCl_3$). The $^1$H NMR spectrum was comparable to that previously reported for the corresponding racemic form.[9]

16. *Synthesis of (+)-(2R,6S)-N,N,N-trimethyl(6-methyl-1,4-dioxan-2-yl)methanaminium iodide, (+)-(2S,6S)-N,N,N-trimethyl(6-methyl-1,4-dioxan-2-yl)methanaminium iodide, (−)-(2S,6R)-N,N,N-trimethyl(6-methyl-1,4-dioxan-2-yl) methanaminium iodide, and (−)-(2R,6R)-N,N,N-trimethyl(6-methyl-1,4-dioxan-2-yl)methanaminium iodide [(+)-(2R,6S)-***1a***, *(+)-(2S,6S)-***1b**, *(−)-(2S,6R)-***1a**, *and (−)-(2R,6R)-***1b***]:* These were prepared following the procedure described in Ref. 9, starting from the corresponding free amines (+)-(2*R*,6*S*)-**4a**, (+)-(2*S*,6*S*)-**4b**, (−)-(2*S*,6*R*)-**4a**, and (−)-(2*R*,6*R*)-**4b**. The physico-chemical characteristics of methiodides (+)-(2*R*,6*S*)-**1a** and (−)-(2*S*,6*R*)-**1a** were comparable to those previously reported.[9] (+)-(2*S*,6*S*)-**1b** was recrystallized from 2-PrOH; mp 217 °C; $[\alpha]_{20}^{D}$ +10.87 (*c* 1, $CH_3OH$). Anal. Calcd for $C_9H_{20}INO_2$: C, 35.89; H, 6.69; N, 4.65. Found: C, 35.99; H, 6.50; N, 4.64; (−)-(2*R*,6*R*)-**1b** was recrystallized from 2-PrOH; mp 217 °C; $[\alpha]_{20}^{D}$ −10.99 (*c* 1, $CH_3OH$). Anal. Calcd for $C_9H_{20}INO_2$: C, 35.89; H, 6.69; N, 4.65. Found: C, 36.22; H, 6.65; N, 4.51. The $^1$H NMR spectra of compounds (+)-(2*S*,6*S*)-**1b** and (−)-(2*R*,6*R*)-**1b** were comparable to that previously reported for the corresponding racemic form.[9]

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