Stereocontrolled Synthesis of *cis*-Dibenzoquinolizine Chlorofumarates: Curare-Like Agents of Ultrashort Duration

Istvan Kaldor, Paul L. Feldman, Robert A. Mook, Jr., John A. Ray, Vicente Samano, Andrea M. Sefler, James B. Thompson, Benjamin R. Travis, and Eric E. Boros*

Division of Medicinal Chemistry, GlaxoSmithKline Research & Development, Five Moore Drive, Research Triangle Park, North Carolina 27709

eeb39577@gsk.com

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The quaternizations of dibenzoquinolizines **9** and **14** with 3-halo-1-propanols are highly *cis*-selective (94−100% *cis*), results consistent with the *N*-methylation of *O*-methylcapaurine (**7b**), but in contrast to the proposed *trans*-stereochemistry of dibenzo[*a*,*h*]quinolizine methiodide **10** and the analogous quaternizations of 1-benzyl- and 1-phenylisoquinoline congeners **5b** and **5c**. In this report, we describe stereoselective preparation of the unique *cis*-dibenzoquinolizinium propanols **15** and **16** and their transformation into bis- and mixed-onium chlorofumarates **19**, **20ab**, and **26**. Dibenzo-[*a*,*g*]quinolizinium propanol **15** was prepared enantioselectively in three steps from dihydroisoquinoline **11**. Asymmetric transfer hydrogenation of **11** in the presence of triethylamine/formic acid and Noyori's chiral ruthenium catalyst **12** produced *R*-(−)-5′,8-dimethoxynorlaudanosine (**13**) in 98% yield and 87% ee**.** Pictet−Spengler cyclization of **13** in formalin/formic acid afforded the dibenzo[*a*,*g*]quinolizine **14** in 65% yield. Quaternization of **14** with 3-chloro-1-propanol under Finkelstein conditions generated *cis*-dibenzoquinolizinium propanol **15** in 85% yield with >94% *cis*-selectivity. The *cis*-dibenzo[*a*,*h*]quinolizinium propanol **16** was obtained as a single stereoisomer by reaction of the known tetramethoxyquinolizine **9** with neat 3-iodo-1-propanol. Bis-onium chlorofumarates **18** and **19** and the mixed-onium derivative **20ab** were prepared by a pool synthesis procedure from (1*R*)-*trans*-**6a**, **16**, and chlorofumaryl chloride (**17**). Mixed-onium α-chlorofumarate **26** was synthesized from (1*S*)-*trans*-**6d**, **15** and (±)-*trans*-2,3-dichlorosuccinic anhydride (**22**), employing a recently disclosed chlorofumarate mixed-diester synthesis. The title compounds (**19**, **20ab**, and **26**) displayed curare-like effects of ultrashort duration in rhesus monkeys.

Introduction

Intravenous administration of the naturally occurring bis-benzylisoquinoline *d*-tubocurarine (curare) (**1**) to induce skeletal muscle relaxation (neuromuscular blockade) during surgical procedures revolutionized the practice of anesthesia.[1] Since that time, a number of synthetic and semisynthetic neuromuscular blockers (NMBs) have been introduced into the clinic with varying time courses of NMB (curare-like) activity. Examples of these adjuncts to anesthesia include the ultra-short-acting NMB succinylcholine[1] (**2**), the short-acting[2] bis-benzyl isoquinoline mivacurium[3] (Mivacron) (**3**), and the long-acting[2] agent doxacurium[4] (Nuromax) (**4**).

Succinylcholine (**2**) is the only rapid onset, ultra-short-acting NMB currently available in the clinic; however, its depolarizing mechanism of action produces a number of unwanted side-effects. Nondepolarizing[1,5] NMBs such as **3** and **4** are devoid of the side-effects typically associated with depolarizing relaxants and anesthesiologists have long recognized the need for a nondepolarizing succinylcholine replacement.

We have been interested in the stereoselective synthesis of ultra-short-acting isoquinoline-based NMBs as possible replacements for succinylcholine. A common problem in the synthesis of **3** and **4** and their congeners is the N-quaternization reaction of tetrahydroisoquinolines **5** which generates a mixture of *cis* and *trans* isoquinolinium propanols (**6**) (eq 1). In this report we describe the stereocontrolled synthesis of conformationally constrained analogues of *trans*-**6b** and *trans*-**6c** and their conversion into the ultra-short-acting curare-like agents **19**, **20ab**, and **26**.

Results and Discussion

Benzylisoquinolinium propanols **6a**[3,6] and **6b**[4] are the penultimate intermediates in the synthesis of **3** and **4**, respectively. Mivacurium (**3**) is derived from (*R*)-5′-

(1) Skeletal muscle relaxants or neuromuscular blockers (NMBs) are adjuncts to anesthesia and are used to provide skeletal muscle relaxation during surgery and to facilitate tracheal intubation. For a review of the chemistry and pharmacology of NMBs and their antagonists, see: Savarese, J. J.; Miller, R. D.; Lien, C. A.; Caldwell, J. E. *Anesthesia*, 4th ed.; Miller, R. D., Ed.; Churchill Livingstone: New York, 1994; pp 417−488.

(2) NMBs are defined by their duration of action as ultrashort (8 min), short (20 min), intermediate (50 min), and long acting (≫ 50 min), see: Bedford, R. F. *Anesthesiology* **1995**, *82*, 33A.

(3) Swaringen, R. A., Jr.; El-Sayad, H. A.; Yeowell, D. A.; Savarese, J. J.; (Wellcome Foundation Ltd. and General Hospital Corp.) Eur. Pat. Appl. EP 181,055, May 14, 1986; *Chem. Abstr.* **1986**, *105*, 172809y.

(4) El-Sayad, H. A.; Yeowell, D. A.; Swaringen, R. A., Jr. (Wellcome Foundation Ltd.) Eur. Pat. Appl. EP 54,309, Jun 23, 1982; *Chem. Abstr.* **1982**, *97*, 163306w.

(5) Nondepolarizing NMBs are nicotinic acetylcholine receptor (NChR) antagonists and depolarizing NMBs are NChR agonists (see ref 1).

(6) El-Sayad, H. A.; Swaringen, R. A.; Yeowell, D. A.; Crouch, R. C.; Hurlbert, S.; Miller, R. W.; McPhail, A. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2067−2077.

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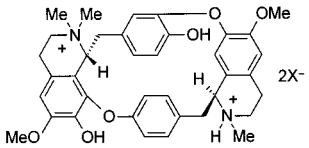
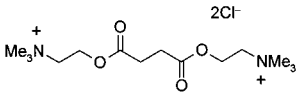
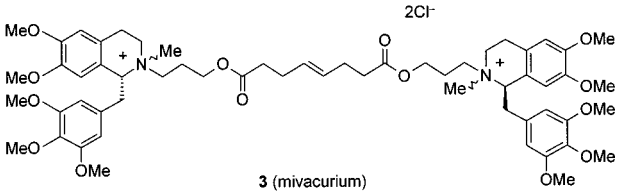


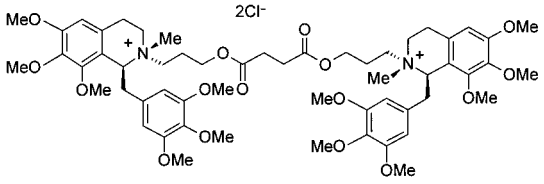
1 (*d*-tubocurarine)



2 (succinylcholine)

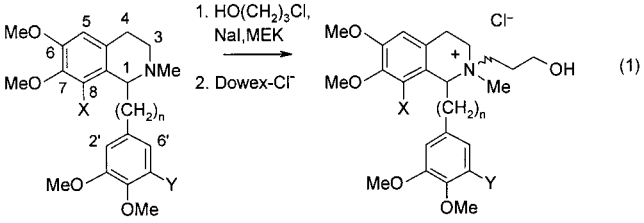


3 (mivacurium)



4 (doxacurium)

methoxylaudanosine ((*R*)-**5a**) while doxacurium (**4**) is obtained from the racemic 5′,8-dimethoxylaudanosine (±)-**5b**. Isoquinolinium propanols **6a** and **6b** are generated as mixtures of *cis* and *trans* stereoisomers (*cis*/*trans* refers to the relationship between the benzylic substituent at C-1 and the 3-hydroxypropyl side chain at N-2) by reaction of the corresponding tetrahydroisoquinolines (**5**) with 3-iodo-1-propanol generated in situ under Finkelstein conditions (*cis*:*trans* ratio ~1:3) (eq 1). In the



(1)

5a: n=1; X=H; Y=OMe
5b: n=1; X=Y=OMe
5c: n=0; X=Y=H
5d: n=0; X=H; Y=OMe

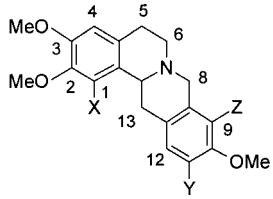
6a-d
cis:*trans* ~ 1:3

synthesis of **3**, the *cis*/*trans* mixture of **6a** is carried through the final coupling stage with octenedioyl chloride whereas the racemate of *trans*-**6b** is first isolated and then reacted with succinyl chloride to give **4**. Mivacurium (**3**) is obtained as a mixture of the *trans-trans, trans-cis,* and *cis-cis* isomers and doxacurium is isolated as a mixture of the *meso* isomer (**4**) and the corresponding *dl*-pair.

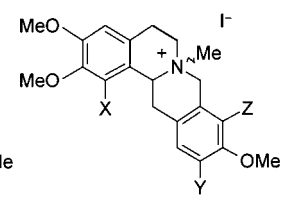
Recent research in our laboratories[7] has focused on the preparation of novel ultra-short-acting[2] nondepolarizing NMBs as potential replacements for succinylcholine. Some of these analogues incorporate 1-aryl tetrahydroisoquinolinium groups (e.g., **6c** and **6d**) linked by a chemically labile chlorofumarate inter-onium diester. The resulting bis-phenylisoquinolines have significantly lower neuromuscular potency relative to their bis-benzylisoquinoline congeners, but produce more rapid onsets of neuromuscular blockade. Interestingly, quaternization of the 1-phenyl isoquinolines **5c** and **5d** with 3-iodo-1-propanol also yield *cis*/*trans* mixtures of the corresponding onium compounds **6c** and **6d** in ratios comparable to those observed for the 1-benzyl analogues **6a** and **6b** (e.g., *cis:trans* ratio ~1:3).

Faced with the moderate stereoselectivity (~75% *trans*) in the formation of **6a**−**d**, we focused part of our synthetic effort on the preparation of conformationally constrained isoquinolines in the hopes of enhancing the stereoselectivity of N-alkylation and perhaps improving biological activity. Accordingly, we embarked on the synthesis of the *cis*-dibenzoquinolizinium propanols **15** and **16** (*cis* with respect to the benzylic methine hydrogen and the 3-hydroxypropyl side chain), as conformationally restricted analogues of the *trans* isomers of **6b** and **6c**, respectively.

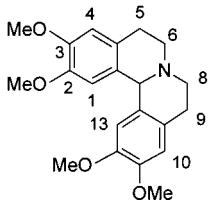
Variable stereoselectivities have been reported for quaternization reactions involving the dibenzoquinolizine family of compounds (e.g., **7** and **9**). For example, N-alkylation of (±)-xylopinine (**7a**) with iodomethane provides a mixture of stereoisomers (**8a**) from which the *trans* isomer was isolated in ca. 51% yield[8] (*trans* with respect to the benzylic methine hydrogen and *N*-methyl substituent). Conversely, *N*-methylation of *O*-methylcapaurine (**7b**) yields exclusively the *cis*-product[9] (*cis*-**8b**) based on IR spectroscopy and ^{13}C NMR. Interestingly, quaternization of the symmetrical dibenzo[*a*,*h*]quinolizine **9** with iodomethane affords a single stereoisomer of **10** that was proposed to have a *trans* relationship between the bridgehead methine hydrogen and *N*-methyl group.[10]



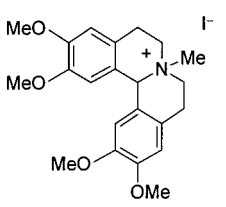
7a: X=Z=H; Y=OMe
7b: X=Z=OMe; Y=H



8a: X=Z=H; Y=OMe
8b: X=Z=OMe; Y=H



9



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Our investigations into the N-quaternization of dibenzoquinolizines **9** and **14** with 3-halo-1-propanols (Scheme 1) have found these reactions to proceed with 94−100% *cis*-stereoselectivity, a result consistent with the *N*-methylation of *O*-methylcapaurine[9] (**7b**) and in contrast to the implied *trans*-stereochemistry of **10**.[10] Stereose-

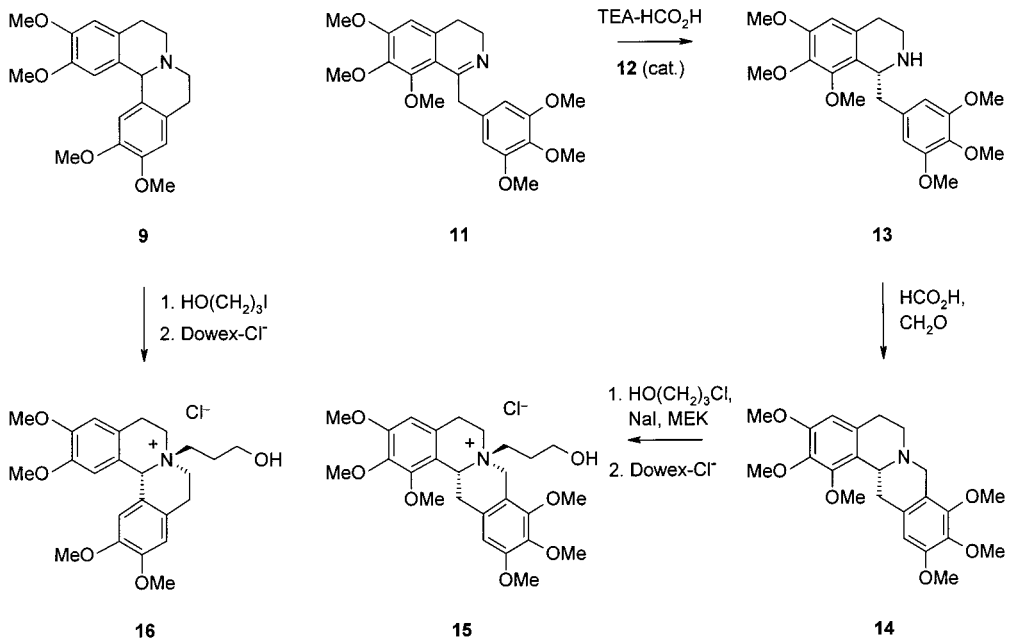
(7) Boros, E. E.; Bigham, E. C.; Boswell, G. E.; Mook, R. A., Jr.; Patel, S, S.; Savarese, J. J.; Ray, J. A.; Thompson, J. B.; Hashim, M. A.; Wisowaty, J. C.; Feldman, P. L.; Samano, V. *J. Med. Chem.* **1999**, *42*, 206−209 and references therein.

(8) Kametani, T.; Huang, S.-P.; Koseki, C.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1977**, *42*, 3040−3046.

(9) Takao, N.; Iwasa, K.; Kamigauchi, M.; Sugiura, M. *Chem. Pharm. Bull.* **1977**, *25*, 1426−1435.

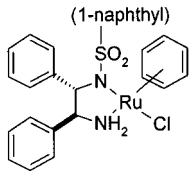
(10) Bishop, D. C.; Tucker, M. J. *J. Chem. Soc. (C)* **1970**, 2184−2186.

Scheme 1



lective preparation of *cis*-dibenzoquinolizinium propanols **15** and **16** and their transformation into bis- and mixed-onium chlorofumarates **19**, **20ab**, and **26** by pool synthesis techniques and chlorofumarate mixed-diester methodology are described herein.

Achiral tetramethoxy dibenzo[*a*,*h*]quinolizine **9** was prepared from 1-(3,4-dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline and bromoacetaldehyde oxime using a published procedure.[10] Asymmetric synthesis of the hexamethoxy dibenzo[*a*,*g*]quinolizine **14** and quaternizations of **9** and **14** employing 3-halo-1-propanols are illustrated in Scheme 1. We wished to prepare the *R*-enantiomer of **14** since the (1*R*)-*trans* configuration of the isoquinolinium moiety generally provides optimum neuromuscular potency.[7,11] Dihydroisoquinoline **11** was prepared from mescaline and 3,4,5-trimethoxyphenylacetyl chloride using standard methods.[12,13] Asymmetric transfer hydrogenation of **11** with triethylamine/formic acid in the presence of Noyori's chiral ruthenium catalyst **12**[14a] provided tetrahydroisoquinoline **13** in 98% yield and



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87% ee as determined by chiral HPLC. Flash chromatography on silica gel followed by recrystallization from Et_2O provided the pure enantiomer. Assignment of the *R*-configuration to (−)-**13** is empirical and is based on the analogous asymmetric synthesis of cryptostyline II utilizing the enantiomer of **12**.[14a] To our knowledge, pure enantiomers of 5′,8-dimethoxynorlaudanosine (**13**) have not been previously described in detail. Pictet−Spengler cyclization[15] of **13** in the presence of formaldehyde provided the requisite dibenzo[*a*,*g*]quinolizine **14** in 65% yield following flash chromatography.

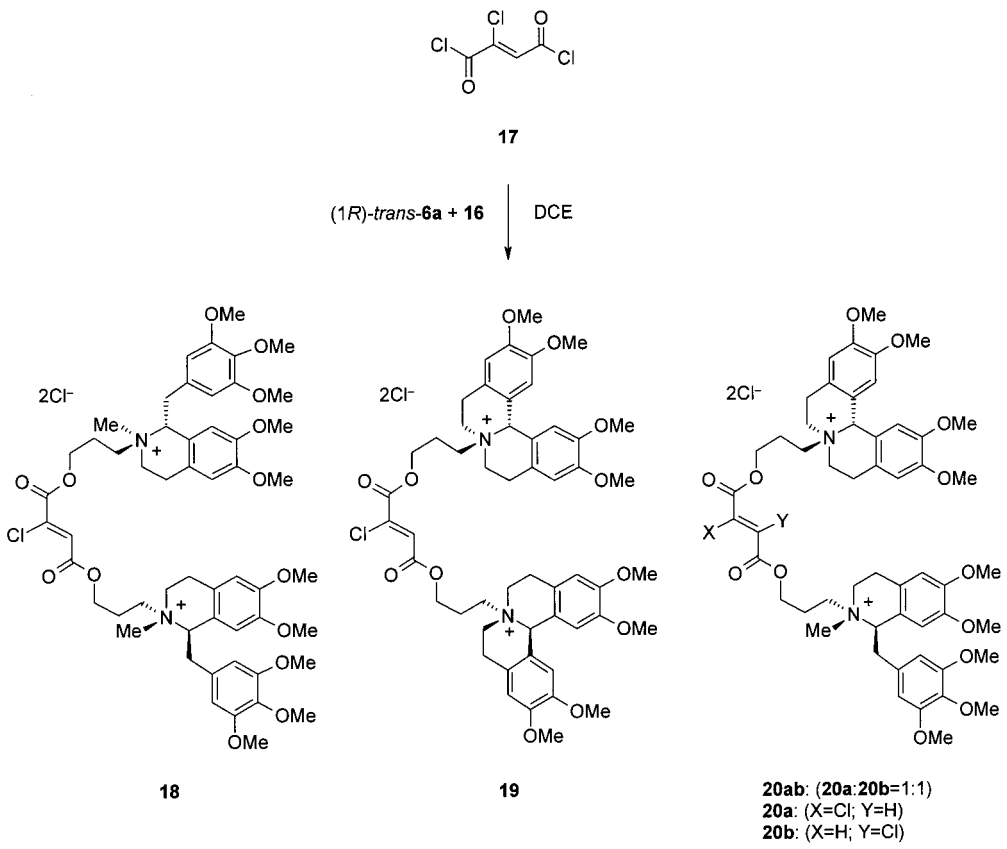
We next turned our attention to the quaternization of dibenzoquinolizines **9** and **14** with 3-halo-1-propanols. Reaction of dibenzo[*a*,*h*]quinolizine **9** with neat 3-iodo-1-propanol provided a single stereoisomer (**16**) in 99% yield. Analysis of the product by 2D ^{1}H NMR NOESY spectroscopy supported a *cis* relationship between the benzylic methine hydrogen and propanol side chain which was also confirmed by X-ray crystal structure analysis (see Supporting Information). On the basis of the *cis*-stereochemistry of **16**, we conclude that the stereochemical relationship between the bridgehead proton and the *N*-methyl group in methiodide **10**[10] is also *cis*.

Alkylation of the dibenzo[*a*,*g*]quinolizine **14** was accomplished with 3-chloro-1-propanol in refluxing methyl ethyl ketone (MEK) in the presence of NaI. Under these conditions, the *cis*-dibenzoquinolizine **15** was obtained in 85% yield with >94% *cis*-selectivity. The *cis*-stereochemistry in **15** was confirmed by 2D ^{1}H NMR ROESY spectroscopy (see Supporting Information).

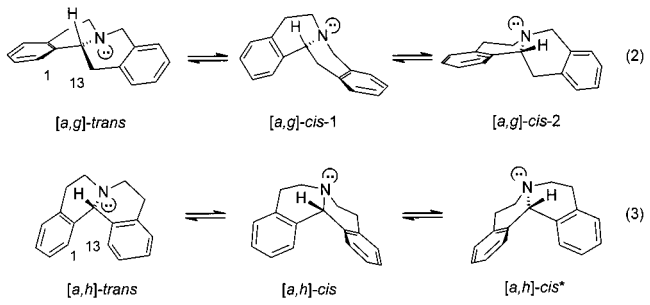
One possible explanation for the high *cis*-stereoselectivity observed in the quaternizations shown in Scheme 1 is that the *cis*-conformers of **9** and **14** (*cis* with respect to the nitrogen lone pair and benzylic methine hydrogen) present less sterically hindered nitrogen lone pairs for the electrophile during the activation process compared to the *trans* forms (eqs 2 and 3).[16,17] However, this

(11) Patel, S. S.; Maehr, R. B.; Savarese, J. J.; Jackson, M. M.; Wastila, W. B.; Wisowaty, J. C. *Eur. J. Pharm. Sci.* **1997**, *5*, 253−266.
(12) Franck, B.; Blaschke, G. *Justus Liebigs Ann. Chem.* **1966**, *695*, 144−157.
(13) Falck, J. R.; Miller, L. L.; Stermitz, F. R. *Tetrahedron* **1974**, *30*, 931−934.
(14) For examples of asymmetric tetrahydroisoquinoline syntheses, see: (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917. (b) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7086−7087. (c) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297−310 and references therein.
(15) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151−206.
(16) Conformational analyses of dibenzo[*a*,*g*]- and dibenzo[*a*,*h*]-quinolizines typically evaluate one *trans* and two *cis* forms (see refs 17a and 17b).

Scheme 2



reasoning does not explain the ca. 51% yield of *trans* product observed in the *N*-methylation of (±)-xylopinine (**7a**).[8]



Assuming no equilibration of *cis*/*trans* isomers under the reaction conditions, the high *cis*-selectivities observed in the N-alkylations of *O*-methylcapaurine (**7b**)[9] and **14** are probably controlled by an intramolecular repulsive interaction between the C-1 methoxy substituent and the C-13 hydrogens in the transition state leading to the *trans* product.[9] This steric interaction, which is alleviated in one of the *cis* conformations,[17a] should raise the energy of activation[18] for the formation of *trans* isomer and therefore increase the proportion of *cis* product. A shift in the conformational equilibrium of C-1-substituted dibenzo[*a*,*g*]quinolizines toward the *cis* forms has been ascribed to this effect.[9,17a] A severe steric interaction also exists between the C-1 and C-13 hydrogens in the rigid *trans* conformer of dibenzo[*a*,*h*]quinolizine **9** (internuclear separation ca. 1 Å based on Dreiding models), and its manifestation during the activation process would further explain the high *cis*-selectivity observed in the N-alkylation of this compound.

With a practical synthesis of the constrained isoquinolinium alkanols **15** and **16** in hand, we pursued their conversion to curare-like agents of ultrashort duration. A chlorofumarate inter-onium linker is known to produce ultrashort duration of NMB effect, and the incorporation of disparate onium nuclei in the same molecule (mixed-onium) can improve neuromuscular potency and diminish unwanted cardiovascular side effects.[7,19] For these reasons, the preparation of bis- and mixed-onium chlorofumarate derivatives of **15** and **16** were of interest.

A pool synthesis of bis-onium chlorofumarates **18** and **19** and mixed-onium chlorofumarate **20ab** was accomplished by reacting chlorofumaryl chloride (**17**)[20] with an equimolar solution of **16** and (1*R*)-*trans*-**6a**[21] in DCE at ambient temperature (Scheme 2). This reaction produced the expected statistical mixture of bis- and mixed-onium products (**18**, **19**, and **20ab**) which were isolated by preparative HPLC. The mixed-onium derivative (**20ab**)

(17) (a) Kametani, T.; Fukumoto, K.; Ihara, M.; Ujiie, A.; Koizumi, H. *J. Org. Chem.* **1975**, *40*, 3280−3283. (b) Vlaeminck, F.; De Cock, E.; Tourwe, D.; Van Binst, G. *Heterocycles* **1981**, *15*, 1213−1218.

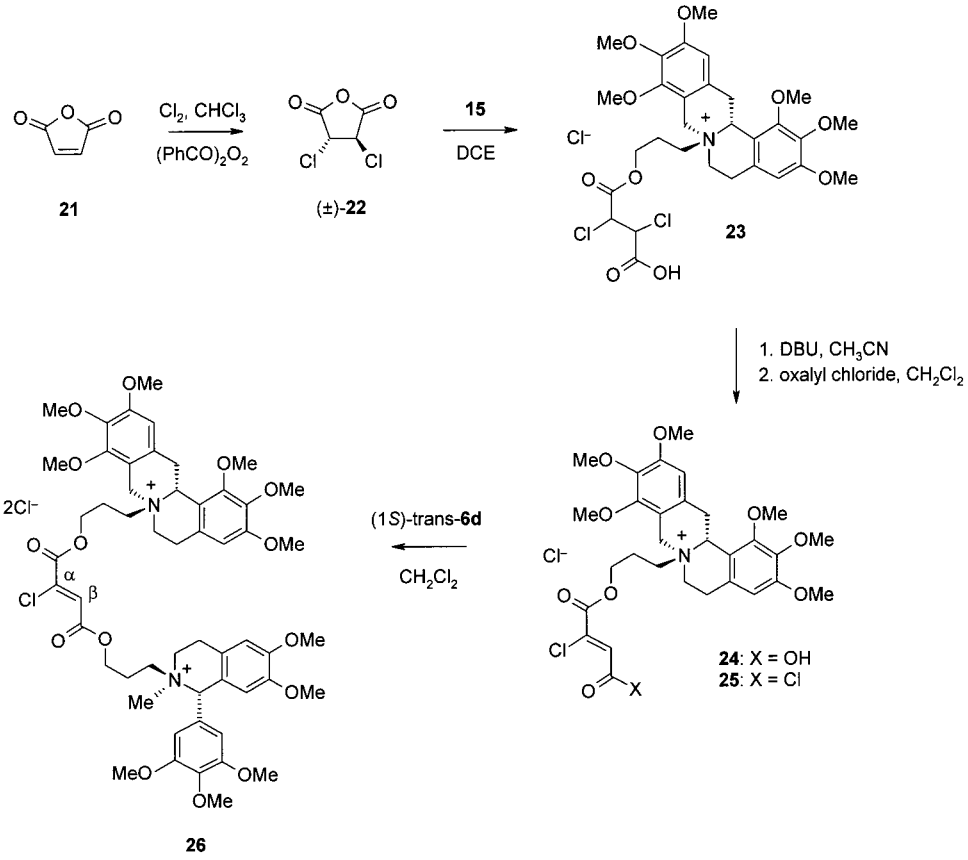
(18) The Curtin−Hammett principle applies to the quaternization of tertiary amines, and the geometry of the dibenzoquinolizine skeleton at the transition state of quaternization should resemble that of the corresponding dibenzoquinolizine conformer, see: Bottini, A. T. *Selective Organic Transformations*, Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1970; pp 89−142.

(19) Bigham, E. C.; Boswell, G. E.; Savarese, J. J.; Swaringen, R. A., Jr.; Patel, S. S.; Boros, E. E.; Mook, R. A., Jr.; Samano, V. (Glaxo Group Ltd. and Cornell Research Foundation Inc.) PCT Int. Appl. WO 98/42675, Oct 1, 1998; *Chem. Abstr.* **1998**, *129*, 275845.

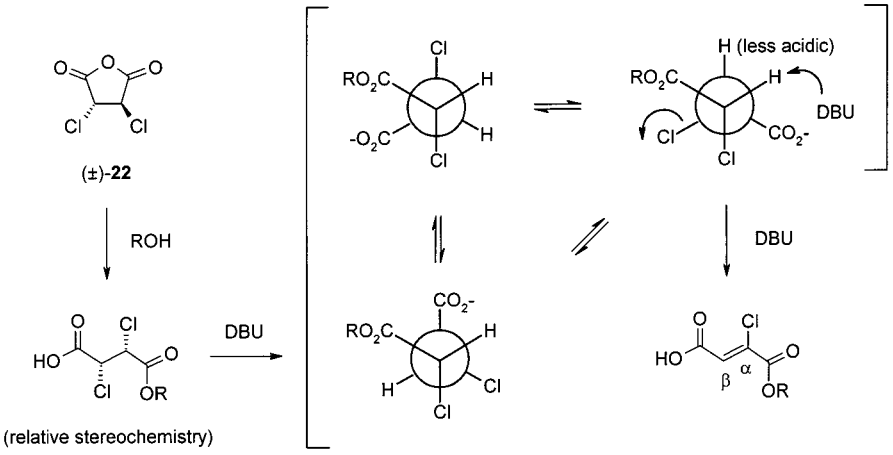
(20) Akhtar, M.; Botting, N. P.; Cohen, M. A.; Gani, D. *Tetrahedron* **1987**, *43*, 5899−5908.

(21) For a preliminary account of the chlorofumarate mixed-diester methodology, see: Samano, V.; Ray, J. A.; Thompson, J. B.; Mook, R. A., Jr.; Jung, D. K.; Koble, C. S.; Martin, M. T.; Bigham, E. C.; Regitz, C. S.; Feldman, P. L.; Boros, E. E. *Org. Lett.* **1999**, *1*, 1993−1996.

Scheme 3



Scheme 4



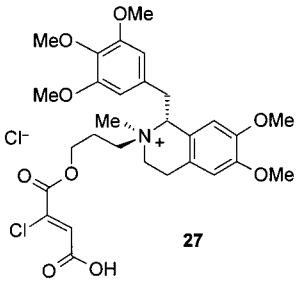
was isolated as a 1:1 mixture of inseparable α- and *β*-chlorofumarate regioisomers (**20a** and **20b**).

The pharmacodynamic evaluation and potential development of any mixed-onium chlorofumarate regioisomer, such as **20a** or **20b**, required a selective synthesis. To achieve the desired chlorobutenedioate geometry and regiochemistry, a selective chlorofumarate mixed-diester synthesis was developed.[21] This practical methodology is exemplified herein by the synthesis of mixed-onium α-chlorofumarate **26** (Scheme 3). Chlorination of maleic anhydride (**21**) in the presence of 0.02 mol % benzoyl peroxide provided *trans*-dichlorosuccinic anhydride **22**[22] in 65% yield as a white hygroscopic solid. Reaction of **22** with quinolizinium propanol **15** in DCE gave the dichlorosuccinate monoester **23** with the necessary stereochemistry to yield the desired chlorofumarate (**24**) upon elimination of HCl. Treatment of **23** with DBU (2 equiv) in acetonitrile induced regio- and stereoselective elimination of HCl and afforded α-chlorofumarate monoester **24** in 34% overall yield from **15** following recrystallization from DCE.

The chlorofumarate regiochemistry in **24** is based on the hypothesis that DBU first abstracts the carboxyl proton of **23**, thereby decreasing the acidity of the hydrogen α to the carboxylate group. This in turn leads to removal of the proton α to the ester carbonyl and loss of chloride α to the carboxylate through an E2 elimination mechanism (Scheme 4). The α-chloro regiochemistry of **24** is also supported by proton−carbon multiple bond

(22) Feuer, H.; Rubinstein, H. *J. Org. Chem.* **1959**, *24*, 811−813.

correlation NMR spectroscopy (HMBC) of the related chlorofumarate monoester **27**, which was prepared by a similar procedure.[21] Conversion of **24** to the mixed onium α-chlorofumarate diester **26** was accomplished by conversion to its acid chloride derivative (**25**) followed by treatment with (1*S*)-*trans*-**6d**.[21]



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Summary

In closing, the novel, conformationally constrained isoquinolinium propanols **15** and **16** were synthesized in good yield and in a stereocontrolled fashion by quaternization of their corresponding dibenzoquinolizines **9** and **14** with 3-halo-1-propanols. The N-quaternization reactions of **9** and **14** are highly *cis*-selective (94−100% *cis*) in contrast to the quaternization of their 1-benzyl- and 1-phenyltetrahydroisoquinoline congeners (**6b** and **6c**) and the *N*-methylation of (±)-xylopinine (**7a**). Moreover, the products (**15** and **16**) incorporate distal hydroxyl groups suitable for further transformation into dicationic skeletal muscle relaxants. Bis- and mixed-onium chlorofumarates **19** and **20ab** were prepared nonselectively from **16** while mixed-onium α-chlorofumarate **26** was obtained from **15** by a regiocontrolled chlorofumarate mixed-diester synthesis. The bis- and mixed-onium chlorofumarates described herein produced curare-like effects of ultrashort duration in rhesus monkeys.[23]

Experimental Section

General. All reagent chemicals were used without purification and yields are unoptimized. Analytical HPLC analyses were performed on 4 × 250 mm 5μ Si60 LiChrosorb columns (E. Merck, Darmstadt, Germany) at a flow rate of 1.6 mL/min. Preparative HPLC separations were performed on twin Porasil (15−20 μm) cartridges (Waters/Millipore, Milford, MA) at a flow rate of 60 mL/min. The mobile phase for analytical and preparative HPLC separations consisted of 0−25% MeOH/CH_2Cl_2 mixtures containing 0.25 mL methanesulfonic acid (MSA)/L. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. All ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz and coupling constants are in Hz. Chemical shifts are reported in ppm relative to the residual protonated solvent resonance of DMSO-d_6 (δ 2.50), $CDCl_3$ (δ 7.24) and acetone-d_6 (δ 2.04). Positive ion flow injection electrospray mass spectra (MS) are reported in the form *m*/*z* (singly or doubly charged positive ion, relative intensity).

The 2′- and 6′-protons on the trimethoxyphenyl substituent of (1*S*)-*trans*-**6d** and its mixed-onium derivative **26** are nonequivalent by ^{1}H NMR (DMSO-d_6) and appear as very broad signals. Heating the sample produces coalescence of these peaks. This phenomenon is also observed for the corresponding 3′- and 5′-methoxy protons and is presumed to result from hindered rotation of the trimethoxyphenyl group.

(1*R*)-6,7,8-Trimethoxy-1-(3,4,5-trimethoxyphenyl)methyl-1,2,3,4-tetrahydroisoquinoline (13). A solution of **11** (3.54 g, 8.82 mmol) in 5:2 formic acid/triethylamine (4 mL) and CH_2Cl_2 (20 mL) was degassed for 5 min with nitrogen, and ruthenium catalyst **12**[14a] (136 mg, 0.22 mmol) was added. The reaction mixture was stirred at room temperature overnight, quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined EtOAc layers were dried over Na_2SO_4, filtered, and concentrated to provide the crude product (3.5 g, 98% yield) as a dark oil. Chiral HPLC analysis (see below) indicated 87% ee and 99% chemical purity. Flash chromatography on silica gel eluting with 10% MeOH/EtOAc followed by recrystallization from Et_2O provided a single enantiomer (**13**) (1.6 g, 45% overall yield) as an off-white solid: $[\alpha]^{25}_D = -34.7°$ (*c* = 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.51 (2H, s), 6.45 (1H, s), 4.30 (1H, dd, *J* = 10, 3), 4.04 (3H, s), 3.90 (9H, s), 3.88 (6H, s), 3.25 (1H, ddd, *J* = 15, 11, 5), 3.11 (1H, dd, *J* = 6, 3), 3.01 (1H, m), 2.80−2.95 (2H, m), 2.65 (1H, br dt, *J* = 15, 3), 1.89 (1H, br); ES$^+$ MS *m*/*z* 404 (M^+, 100), 222 (55); HPLC: one major peak (100%) at 9.44 min (Daicel Chiralcel OD-H column, eluent 30% IPA/hexane/0.1% TEA).

(*R*)-1,2,3,9,10,11-Hexamethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine (14). A mixture of **13** (150 mg, 0.37 mmol), 37% formalin (1 mL), and 96% formic acid (0.5 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, basified with NaOH solution, and extracted with EtOAc. The EtOAc extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. Flash chromatography on silica gel eluting with 2% MeOH/CH_2Cl_2 gave **14** as an oil (100 mg, 65% yield): $[\alpha]^{25}_D = +229.9°$ (*c* = 0.575, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 6.42 (2H, s), 4.07 (1H, d, *J* = 16), 3.88 (3H, s), 3.87 (3H, s), 3.85 (3H, s), 3.83 (6H, s), 3.81 (3H, s), 3.88−3.81 (2H, obscured), 3.42 (1H, dd, *J* = 16, 3), 3.08 (1H, m), 2.99 (1H, m), 2.80−2.60 (3H, m); HPLC: one major peak (97%) at 2.89 min (Altima C-18 column, eluent 70−100% CH_3CN/H_2O/0.1% TEA); HRMS $(M + H)^+$ calcd for $C_{23}H_{30}NO_6$: 416.2074. Found: 416.2027.

(7*S*,13a*R*)-1,2,3,9,10,11-Hexamethoxy-7-(3-hydroxypropyl)-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizinium Chloride (15). A mixture of **14** (720 mg, 1.73 mmol), NaI (1.04 g, 6.93 mmol), Na_2CO_3 (92 mg, 0.865 mmol), and 3-chloro-1-propanol (655 mg, 6.93 mmol) in MEK (10 mL) was heated at reflux for 48 h. The solvent was removed at reduced pressure, and the resulting material was dissolved in water and extracted with EtOAc to remove excess 3-chloro-1-propanol. The aqueous layer was saturated with NaCl and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and concentrated. The solid was redissolved in water and stirred for 15 min over Dowex 1 × 8−50 ion-exchange resin. The resin was removed by filtration, and the filtrate was saturated with NaCl and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and concentrated to yield **15** (500 mg) as a rigid foam. Back-extraction of the original EtOAc layers with water and workup of the aqueous phase as described above with Et_2O in place of EtOAc provided an additional 250 mg of **15** (85% combined yield): $[\alpha]^{25}_D = +94°$ (*c* = 0.69, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 6.78 (1H, s), 6.75 (1H, s), 4.96 (1H, dd, *J* = 11, 5), 4.78 (1H, br t, *J* = 5), 4.76 (1H, d, *J* = 16), 4.64 (1H, d, *J* = 16), 3.90 (3H, s), 3.85 (3H, s), 3.80 (3H, s), 3.76 (6H, s), 3.73 (3H, s), 3.66 (2H, m), 3.47 (2H, m), 3.38 (2H, m), 3.22 (1H, dd, *J* = 18, 5), 3.14 (2H, m), 2.99 (1H, dd, *J* = 18, 11), 2.03 (1H, m), 1.90 (1H, m); HPLC: one major peak (95%) at 10.54 min (BDS-hypersil C-8 column, eluent 30−50% CH_3CN/H_2O/0.1% TEA); HRMS (M^+) calcd for $C_{26}H_{36}NO_7$: 474.2493. Found: 474.2483.

7-(3-Hydroxypropyl)-5,8,9,13b-tetrahydro-2,3,11,12-tetramethoxy-6*H*-dibenzo[*a*,*h*]quinolizinium Chloride (16). A solution of **9**[10] (4.00 g, 11.20 mmol) in 3-iodo-1-propanol (20 mL) was stirred at 100 °C for 20 min. The solution was diluted with Et_2O and stirred for 12 h. The iodide of **16** precipitated from solution as a white solid and was collected by filtration (6.08 g, 99% yield): ES$^+$ MS *m*/*z* 414 (M^+, 20), 356 (100); ^{1}H NMR (DMSO-d_6) δ 6.93 (2H, s), 6.75 (2H, s), 5.69 (1H, s), 4.77 (1H, t, *J* = 5), 3.76 (6H, s), 3.73 (4H, m), 3.66 (6H, s), 3.44 (4H, m), 3.08 (4H, m), 1.99 (2H, m). A portion of this material (3.00 g, 5.50 mmol) was dissolved in water (100 mL) and

(23) The NMB activity of **18** in rhesus monkeys has been described in detail (see ref 7).

stirred over Dowex 1 × 8−50 ion-exchange resin (50 g) for 2 h. The mixture was filtered, and the filtrate was saturated with NaCl and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated to provide **16** (2.21 g, 74% yield) as an off-white foam: Anal. Calcd for $C_{24}H_{32}ClNO_5 \cdot (0.7\ H_2O)$: C, 62.32; H, 7.28; N, 3.03. Found: C, 62.32; H, 7.30; N, 3.14. A crystal of **16** suitable for X-ray analysis was obtained by recrystallization from water.

Pool Synthesis of 18, 19, and 20ab. Chlorofumaryl chloride (**17**)[20] (0.95 g, 5.00 mmol) was added to a stirred solution of **16** (2.21 g, 4.9 mmol) and (1*R*)-*trans*-**6a**[21] (2.4 g, 4.9 mmol) in 1:4 $CHCl_3$/1,2-dichloroethane (125 mL), and the reaction was stirred 30 min at room temperature. The solvent was removed at reduced pressure and the products were separated by preparative HPLC (see General Experimental Section). Fractions containing the desired compound were diluted with $CHCl_3$ and *partially* concentrated to remove the MeOH (note: bis- and mixed-onium chlorofumarate diesters are susceptible to transesterification). The remaining $CHCl_3$ solution was washed with 1:1 brine/water, dried over Na_2SO_4, filtered, and concentrated. Lyophilization from water provided **19** (0.97 g, 18% yield) and **20ab** (1.4 g, 27% yield) as white powders. The synthesis and characterization of **18** have been described.[7]

(*Z*)-2-Chloro-bis{3-(5,8,9,13b-tetrahydro-2,3,11,12-tetramethoxy-6*H*-dibenzo[*a*,*h*]-7-quinolizinio)propyl}-2-butenedioate Dichloride (19). ^{1}H NMR (DMSO- d_6) δ 7.09 (1H, s), 6.91 (4H, s), 6.73 (2H, s), 6.72 (2H, s), 5.78 (1H, s), 5.75 (1H, s), 4.25 (4H, m), 3.80 (8H, m), 3.74 (12H, s), 3.64 (12H, s), 3.55 (4H, m), 3.08 (8H, m), 2.28 (4H, m); ES$^+$ MS *m*/*z* 471 (M^{2+}, 100), 356 (10). Anal. Calcd for $C_{52}H_{63}Cl_3N_2O_{12} \cdot (5\ H_2O)$: C, 56.54; H, 6.66; N, 2.53. Found: C, 56.53; H, 6.58; N, 2.53.

(*Z*)-2-Chloro-4-{3-(5,8,9,13b-tetrahydro-2,3,11,12-tetramethoxy-6*H*-dibenzo[*a*,*h*]-7-quinolizinio)propyl}-1-{3-{(1*R*,2*S*)-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-2-isoquinolinio}propyl}-2-butenedioate Dichloride and (*Z*)-2-Chloro-1-{3-(5,8,9,13b-tetrahydro-2,3,11,12-tetramethoxy-6*H*-dibenzo[*a*,*h*]-7-quinolizinio)propyl}-4-{3-{(1*R*,2*S*)-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-2-isoquinolinio}propyl}-2-butenedioate Dichloride (1:1) (20ab). ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, s), 7.64 (1H, s), 6.77 (2H, s), 6.76 (2H, s), 6.62 (6H, m), 6.49 (2H, s), 6.46 (2H, s), 5.96 (1H, s), 5.83 (1H, s), 5.75 (1H, s), 5.73 (1H, s), 5.18 (1H, br d, J = 9.1), 5.06 (1H, br d, J = 7.8), 4.30 (8H, m), 4.05 (8H, m), 3.88 (12H, s), 3.83 (6H, s), 3.82 (6H, s), 3.80 (12H, m), 3.77 (6H, s), 3.76 (6H, s), 3.74 (6H, s), 3.72 (12H, s), 3.39 (6H, s), 3.40−3.10 (14H, m), 2.78 (2H, m), 2.60−2.30 (8H, m); ES$^+$ MS *m*/*z* 487 (M^{2+}, 100), 315 (20). Anal. Calcd for $C_{53}H_{67}Cl_3N_2O_{13} \cdot (4.5\ H_2O)$: C, 56.46; H, 6.79; N, 2.48. Found: C, 56.45; H, 6.62; N, 2.48.

(±)-*trans*-2,3-Dichlorosuccinic Anhydride (22). A solution of maleic anhydride (**21**) (10.6 g, 108 mmol) and benzoyl peroxide (5 mg, 0.02 mmol) in $CHCl_3$ (250 mL) was saturated with chlorine gas, and the resulting yellow solution was stirred for 5 h at room temperature. The mixture was degassed with nitrogen and the product (**22**) crystallized from solution and was collected by filtration as a white solid (11.9 g, 65% yield): mp 90−92 °C; ^{1}H NMR (acetone-d_6) δ 5.68 (2H, s); Anal. Calcd for $C_4H_2Cl_2O_3$: C, 28.43; H, 1.19; Cl, 41.97. Found: C, 28.29; H, 1.32; Cl, 41.90.

(*Z*)-2-Chloro-1-{3-{(7*S*,13a*R*)-1,2,3,9,10,11-Hexamethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]-7-quinolizinio}-propyl} Hydrogen-2-butenedioate Monochloride (24). Dichlorosuccinic anhydride **22** (400 mg, 2.37 mmol) was added portionwise to a predried solution of **15** (690 mg, 1.35 mmol) in DCE (8 mL) over 3 Å molecular sieves. After stirring at room temperature for 3 d, the sieves were removed by filtration, and the filtrate was concentrated at reduced pressure. The crude material was triturated with Et_2O and dried under high vacuum to provide the dichlorosuccinate monoester **23** (950 mg, 98% yield) as a yellow foam. A solution of **23** (900 mg, 1.33 mmol) in CH_3CN (8 mL) was cooled to 0 °C and DBU (425 mg, 2.79 mmol) in CH_3CN (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to room temperature. The solvent was evaporated at reduced pressure, and the resulting material was dissolved in $CHCl_3$ and washed with a 2:1 brine/water containing 5 μL of MSA/mL. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Recrystallization from DCE afforded **24** as a hygroscopic white solid (290 mg, 34% yield): ^{1}H NMR (DMSO-d_6) δ 7.16 (1H, s), 6.750 (1H, s), 6.745 (1H, s), 4.98 (1H, dd, J = 11, 5), 4.81 (1H, d, J = 16), 4.66 (1H, d, J = 16), 4.25 (2H, br t, $J\sim$ 5), 3.89 (3H, s), 3.85 (3H, s), 3.78 (3H, s), 3.77 (1H, m), 3.75 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 3.69 (1H, m), 3.58−3.40 (2H, m), 3.22 (1H, dd, J = 18, 5), 3.16 (2H, m), 3.00 (1H, dd, J = 18, 11), 2.35 (1H, m), 2.18 (1H, m), (carboxyl proton not found); HPLC: one major peak (95%) at 2.04 min (LiChrosorb Si60 column, eluent 6% MeOH/CH_2Cl_2/0.25 mL MSA/L); HRMS (M^+) calcd for $C_{30}H_{37}NO_{10}Cl$: 606.2106. Found: 606.2063.

(*Z*)-2-Chloro-4-{3-[(1*S*,2*R*)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-2-isoquinolinio]-propyl}-1-{3-{(7*S*,13a*R*)-1,2,3,9,10,11-hexamethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]-7-quinolizinio}propyl}-butenedioate Dichloride (26). Chlorofumarate monoester **24** (255 mg, 0.397 mmol) was dissolved in CH_2Cl_2 (3 mL), and oxalyl chloride (1 mL, 11.46 mmol) was added followed by DMF (1 drop). The reaction mixture was stirred for 2.5 h at room temperature, concentrated at reduced pressure, and dried under high vacuum. The resulting acid chloride (**25**) was dissolved in CH_2Cl_2 (3 mL), and a solution of (1*S*)-*trans*-**6d**[21] (241 mg, 0.516 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight, the solvent was removed at reduced pressure, and the product was purified by preparative HPLC as described for the synthesis of **19** and **20ab**. Mixed-onium chlorofumarate **26** was isolated as a white powder (152 mg, 37% yield): ^{1}H NMR (DMSO-d_6) δ 7.19 (1H, br), 7.13 (1H, s), 6.93 (1H, s), 6.76 (1H, s), 6.74 (1H, s), 6.34 (1H, s), 6.08 (1H, br), 5.79 (1H, s), 5.01 (1H, dd, J = 10.9, 5.5), 4.85 (1H, d, J = 15.8), 4.68 (1H, d, J = 15.8), 4.26 (4H, m), 3.89 (3H, s), 3.84 (3H, s), 3.76 (6H, s), 3.75 (3H, s), 3.73 (6H, s), 3.70 (4H, m), 3.68 (3H, s), 3.60−3.80 (6H, br), 3.55 (3H, s), 3.60−3.40 (4H, m), 3.30−3.10 (5H, m), 3.00 (1H, dd, J = 18, 11), 2.83 (3H, s), 2.35 (2H, m), 2.27 (3H, s), 2.18 (2H, m); ES$^+$ MS *m*/*z* 510 (M^{2+}, 100), 413 (30). Anal. Calcd for $C_{54}H_{69}Cl_3N_2O_{15} \cdot (5.5\ H_2O)$: C, 54.43; H, 6.77; N, 2.35. Found: C, 54.39; H, 6.65; N, 2.32.

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Supporting Information Available: 2D ^{1}H NMR ROESY spectra of **15** and X-ray crystal data for **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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