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Synthesis of Ultra-Short-Acting Neuromuscular Blocker GW 0430: A Remarkably Stereo- and Regioselective Synthesis of Mixed Tetrahydroisoquinolinium Chlorofumarates

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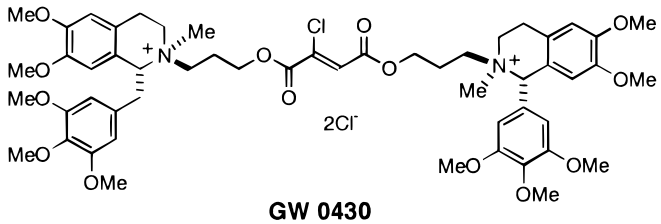
ABSTRACT



GW 0430

The stereo- and regioselective synthesis of ultra-short-acting nondepolarizing neuromuscular blocker GW 0430 (5a) is described. Key steps involved the enantioselective transfer hydrogenation of imine 8 employing Noyori's catalyst, the stereoselective crystallization and methanolysis of *trans*-betaines 11 and 12, and the stereo- and regioselective *trans* elimination of hydrogen chloride from 14. The latter transformation allowed complete control of the position of the chloro substituent and stereochemistry at the double bond of the linker in 15.

Neuromuscular blockers (NMBs) are widely used in anesthesia to provide skeletal muscle relaxation during surgery and facilitate intubation of the trachea. Nondepolarizing NMBs are a highly desirable class due to their excellent clinical and safety profiles.[1] NMBs possessing an ultra-short duration of action are required in emergency, routine surgical, and postoperative settings.[2] Presently, there is no ultra-short-acting nondepolarizing NMB in clinical use.[1a] Herein we describe the stereo- and regioselective synthesis of GW 0430 (**5a**), a novel nondepolarizing ultra-short-acting NMB that is undergoing clinical development.

As part of a program to discover an ultra-short-acting nondepolarizing NMB, we synthesized a mixture of the bistetrahydroisoquinolinium chlorofumarates and mixed tetrahydroisoquinolinium chlorofumarates **5**−**7** via the nonselective route illustrated in Scheme 1. Included in this mixture was a mixed tetrahydroisoquinolinium chlorofumarate (**5ab**, Scheme 4) isolated as a 1:1 mixture of inseparable regioisomers. Preclinical studies demonstrated that **5ab** is a potent ultra-short-acting nondepolarizing NMB (ED_{95} 0.2 mg/kg) in the rhesus monkey.[3] To evaluate the pharmacological properties of **5a** and **5b** separately, a highly stereo- and

(1) (a) Kopman, A. *J. Clin. Anesth.* **1993**, *5*, 39S−45S. (b) Savarese, J. J.; Miller, R. D.; Lien, C. A.; Caldwell, J. E. Pharmacology of Muscle Relaxants and Their Antagonists. In *Anesthesia*, 4th ed.; Miller R. D., Ed.; Churchill Livingstone: New York, 1994; pp 417−488.

(2) Bevan, D. R. *Pharmacol. Toxicol.* **1994**, *74*, 3−9.

(3) 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.

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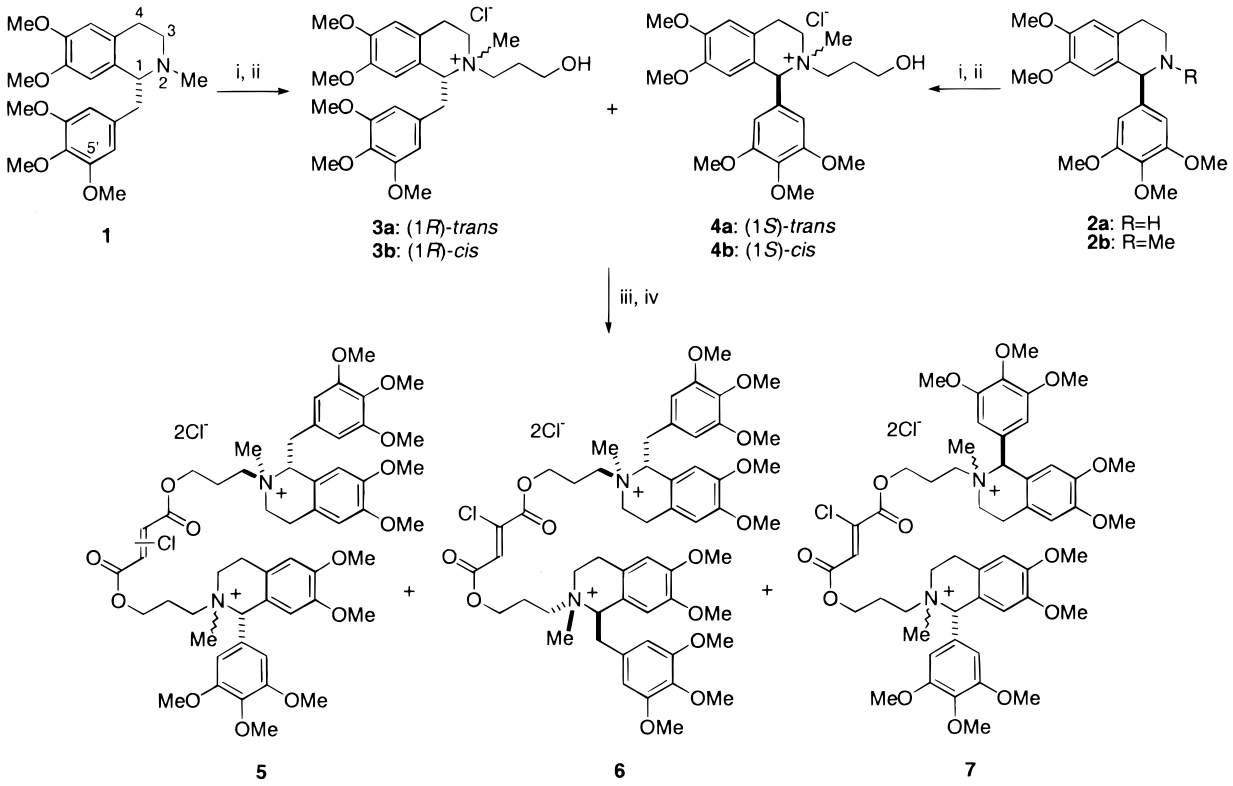
Scheme 1. Nonselective Synthesis of Bis- and Mixed Onium Chlorofumarates **5**, **6**, and **7**



(i) 3-Chloro-1-propanol, NaI, Na_2CO_3, 2-butanone. (ii) Dowex-1-chloride, H_2O. (iii) Compound **3** was enriched in its *trans*-isomer (**3a**) by preparative HPLC prior to use. (iv) Chlorofumaryl chloride, 1,2-dichloroethane.

regioselective synthesis of these mixed tetrahydroisoquinolinium chlorofumarates was developed.

The nonselective synthesis of bisonium chlorofumarates and mixed onium chlorofumarates **5**−**7** (Scheme 1) commenced by reacting in parallel enantiopure (*R*)-(−)-5′-methoxylaudanosine[4] (**1**) and (*S*)-(+)-cryptostyline III[5] (**2b**) with 3-chloro-1-propanol and sodium iodide in refluxing 2-butanone.[6] This provided *trans/cis* mixtures (*trans/cis* refers to the relationship of the 1-benzyl or 1-phenyl substituent and the 3-hydroxy-1-propyl chain at N-2) of the corresponding quaternary ammonium iodides in ∼3:1 ratios, as indicated by ^{1}H NMR spectroscopy and HPLC analysis. Ion exchange followed by preparative HPLC (12% methanol/dichloromethane/0.25 mL of methanesulfonic acid/L) provided (1*R*)-*trans*-1-benzyl headgroup **3a** (∼95% *trans*) in 35% yield. The (1*S*)-*trans*/*cis*-1-phenyl mixture **4ab** was used in the next step without further purification. An equimolar mixture of **3a** and **4ab** in 1,2-dichloroethane was treated with 1 equiv of chlorofumaryl chloride[7] at ambient temperature to provide a statistical mixture of bisonium chlorofumarate and mixed onium chlorofumarate diesters **5**−**7**. Title compounds **5ab** were the major products isolated in 15% yield by preparative HPLC as an inseparable 1:1 mixture of chlorofumarate regioisomers.[8]

Three significant synthetic hurdles had to be overcome to develop a stereo- and regioselective synthesis of **5a** and **5b**. The first obstacle was the development of an efficient enantioselective synthesis of (*S*)-(+)-cryptostyline III[5] (**2b**). While (*R*)-(−)-5′-methoxylaudanosine[4] (**1**) is readily available, **2b** is prepared in low yield by a tedious classical resolution[5] and *N*-methylation sequence starting from racemic **2a**. We prepared **2a** via an efficient asymmetric transfer hydrogenation of 1-phenyl-3,4-dihydroisoquinoline **8**[9] (Scheme 3) employing Noyori's ruthenium catalyst **9** in the presence of formic acid and triethylamine.[10] Chiral HPLC analysis (Chiralpak AS, isopropyl alcohol/hexane/triethylamine) of the crude reaction mixture showed the desired product **2a** in 83% ee and this was further improved when the formic

(4) (a) Stenlake, J. B.; Waigh, R. D.; Dewar, G. H.; Hughes, R.; Chapple, D. J.; Coker, G. G. *Eur. J. Med. Chem.* **1981**, *16*, 515−524. (b) Swaringen, R. A., Jr.; El-Sayad, H. A.; Yeowell, D. A.; Savarese, J. J. (Burroughs Wellcome Co., General Hospital Corporation) U. S. Patent 4,761,418; Aug 2, 1988.

(5) Brossi, A.; Teitel, S. *Helv. Chim. Acta* **1971**, *54*, 1564−1571.

(6) 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.

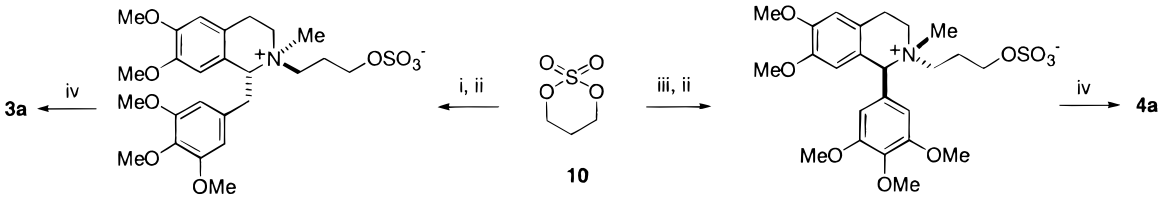
(7) Akhtar, M.; Botting, N. P.; Cohen, M. A.; Gani, D. *Tetrahedron* **1987**, *43*, 5899−5908.

(8) Determined by ^{1}H NMR spectroscopy. The vinylic hydrogen for each chlorofumarate regioisomer **5a** and **5b** appeared at 7.12 and 7.16 ppm, respectively, as distinct singlets.

(9) Prepared by Bishler−Napieralski cyclization as described in Whaley and Govindachari: Whaley, K. W.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74−150.

(10) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917. (b) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297−310 and references therein.

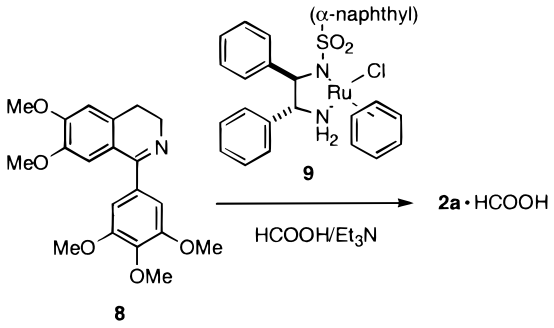
Scheme 2. Synthesis, Stereoselective Crystallization, and Methanolysis of *trans*-Betaines **11** and **12**



(i) **1**, acetone, 65°C. (ii) Crystallization. (iii) **2b**, MeCN, 65°C. (iv) AcCl/MeOH.

acid salt of **2a** precipitated from the reaction mixture in 76% yield and 99% ee. Eschweiler−Clarke methylation of **2a** with formic acid and formalin[11] gave the *N*-methyl derivative **2b** (96%).

Scheme 3. Asymmetric Transfer Hydrogenation of Imine **8**



The second issue to address was the stereoselective preparation of *trans* quaternary headgroups **3a** and **4a**. *Cis*/*trans* mixtures obtained by alkylation of **1** and **2b** with 3-chloro-1-propanol/sodium iodide are difficult to separate even after repetitive chromatography on silica gel. Attempts to improve the *trans* selectivity in the alkylation[12] of **1** and **2b** by modifying the leaving group and the reaction conditions were unsuccessful. In the course of these studies, we discovered that **1** and **2b** were readily quaternized with 1,3-dioxa-2-thiane 2,2-dioxide[13] (**10**) to give the corresponding *trans*/*cis* betaines in a 3:1 ratio (Scheme 2). Although the diastereoselectivity was not improved, we were gratified to discover that the desired (1*R*)-*trans* (**11**) and (1*S*)-*trans* (**12**) betaines crystallized selectively from acetone and acetonitrile, respectively, in good yield (60−69%) and excellent de (98−99%). Methanolysis of betaines **11** and **12** under acidic conditions (acetyl chloride, methanol) provided the required headgroups **3a** and **4a**, quantitatively.

With enantio- and diastereomerically pure **3a** and **4a** in hand, we proceeded to develop a regio- and stereoselective synthesis of mixed onium chlorofumarates **5a** and **5b**. Ring opening of cyclic anhydrides with alcohols[14] and subsequent esterification of the free carboxyl group is a general procedure for preparing mixed diesters. We envisaged that ring opening of (±)-2,3-dichlorosuccinic anhydride[15] [(±)-**13**] with **3a** would generate the 1,2-dichlorosuccinate monoester **14** with the necessary stereochemistry to yield the *trans* double bond in **15** upon E_2 elimination of hydrogen chloride (Scheme 4). We also anticipated that the methine proton adjacent to the ester would be more acidic than the methine proton adjacent to the resulting carboxylate anion in **14** allowing the regioselective abstraction and elimination of hydrogen chloride upon treatment with base. Accordingly, (±)-**13**[15] was reacted with **3a** in dichloromethane at ambient temperature to provide the corresponding monoester **14**. Treatment of **14** with 2 equiv of triethylamine in dichloromethane effected stereo- and regioselective elimination of hydrogen chloride to provide **15** as a single isomer in 86% overall yield. The ^{1}H NMR of **15** shows a singlet at 7.15 ppm for the vinylic hydrogen. COSY and proton−carbon multiple bond correlation (HMBC) NMR experiments with **15** support the *trans* geometry and position of the chlorine α to the ester carbonyl. The final steps involved conversion of **15** to its corresponding acid chloride (oxalyl chloride, dichloromethane) followed by coupling with **4a** to give **5a** as a single regioisomer in 84% yield (90% pure by HPLC). Analytically pure material was obtained by preparative HPLC and lyophilization from water. Regioisomer **5b** was synthesized through a similar sequence which involved ring opening of (±)-2,3-dichlorosuccinic anhydride [(±)-**13**] with **4a**, followed by stereo- and regioselective hydrogen chloride elimination, acid chloride formation, and coupling with **3a**.

The NMB properties of **5a** and **5b** were evaluated and revealed that **5a** was ∼4-fold more potent than **5b** and

(11) Kaluszyner, A.; Galun, A. B. *J. Org. Chem.* **1961**, *26*, 3536−3537.

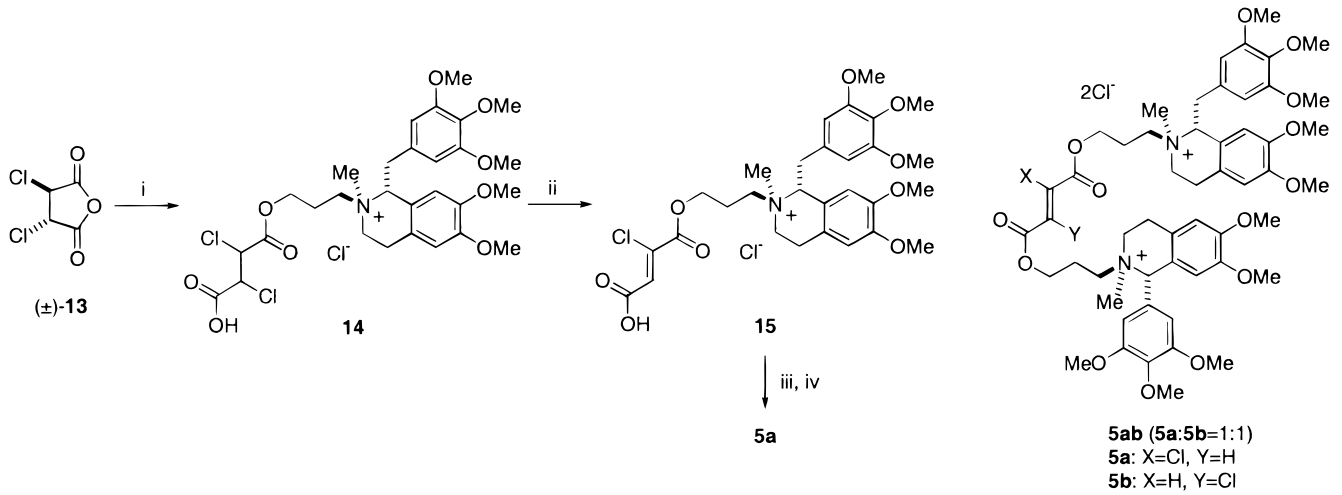
(12) For NMR and X-ray stereochemical studies on quaternization of 1-benzyltetrahydroisoquinolines, see: (a) Stenlake, J. B.; Williams, W. D.; Dhar, N. C.; Marshall I. G. *Eur. J. Med. Chem.* **1974**, *9*, 233−238. (b) Ribar, B.; Lazar, D.; Kalman, A.; Kobor, J.; Bernath, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1141−1144. (c) Lindon, J. C.; Ferrige, A. G. *Tetrahedron* **1980**, *36*, 2157−2159. (d) 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 and references therein.

(13) Cyclic sulfate **10** was prepared from 1,3-propanediol as described in Gao et al.: (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539. (b) Guijarro, D.; Guillena, G.; Mancheno, B.; Yus, M. *Tetrahedron* **1994**, *50*, 3427−3436.

(14) Cox, A. Dicarboxylic and Polycarboxylic Acids. In *Comprehensive Organic Chemistry*, 1st ed.; Sutherland, I. O. Ed.; Pergamon Press: Oxford, 1979; pp 685−690.

(15) Prepared by a modified procedure as described in Feuer et al.: (a) Feuer, H.; Rubinstein, H. *J. Org. Chem.* **1959**, *24*, 811−813. (b) Erickson, L. E. *J. Am. Chem. Soc.* **1965**, *87*, 1867−1875.

Scheme 4. Selective Synthesis of Mixed Onium Chlorofumarate **5a**



(i) **3a**, CH_2Cl_2, amb. temp. (ii) Et_3N, -20°C, CH_2Cl_2. (iii) $(COCl)_2$, CH_2Cl_2. (iv) **4a**, CH_2Cl_2.

displayed a rapid onset of action at its ED_{95} dose and ultrashort duration of NMB effect.[3]

In summary, we have developed a highly efficient stereo- and regioselective synthesis of chlorofumarates **5a** and **5b**. We applied the Noyori procedure to the enantioselective synthesis of (*S*)-(+)-cryptostyline III (**2b**). Quaternization of **1** and **2b** with cyclic sulfate **10** followed by crystallization and methanolysis gave the required *trans* headgroups **3a** and **4a** without the use of chromatography. A stereo- and regioselective *trans* elimination of hydrogen chloride from monoester **14** allowed complete control of the position of the chloro substituent and stereochemistry at the double bond of the linker. A full account on the clinical evaluation of **5a** and the structure−activity relationships of this new class of NMBs will be the subject of future publications.

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Supporting Information Available: Experimental procedures, analytical data (^{1}H NMR, MS, elemental analysis) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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