Organic Process Research & Development **1997**, *1,* 198–210

Development of a Manufacturing Process for Zatosetron Maleate

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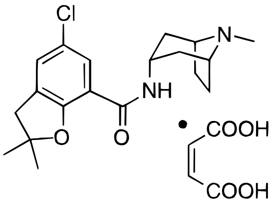
Abstract:

Zatosetron maleate is a potent, selective 5-hydroxytryptamine receptor antagonist. In anticipation of commercialization, a manufacturing synthesis of zatosetron from tropinone and 5-chlorosalicylic acid was developed. Development efforts focused on addressing several key issues including the supply and quality of the critical raw material tropinone, improvements in the stereoselective formation of 3-*endo*-tropanamine, and the compatibility with existing manufacturing capabilities of process requirements for the Claisen rearrangement used to produce a crucial benzofuran intermediate. The results of these studies and an improved route to zatosetron maleate are described.

Introduction

Serotonin is a major neurotransmitter in the central nervous system for which multiple distinct receptor subtypes exist. The $5HT_3$ (5-hydroxytryptamine) receptor subtype has attracted considerable attention with the identification of selective antagonists of these receptors. Zatosetron has been identified as a potent, orally available, long-acting, selective $5HT_3$ receptor antagonist, which is potentially useful in the treatment of central nervous system disorders such as emesis induced by oncolytic drugs, migraine, dementia, anxiety, schizophrenia, and substance abuse.[1,2] Zatosetron maleate (**1**) has been studied for its clinical efficacy against migraine, anxiety, and age-associated memory impairment. While clinical studies were in progress, a manufacturing synthesis was developed in order to support the production of potential bulk quantities in anticipation of market requirements.



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A preparation of zatosetron has been published.[2] While the published synthesis, which is presented in Scheme 1, afforded a completely satisfactory strategy for assembling the molecular entity, it had not been optimized for producing commercial quantities of bulk drug substance (10 synthetic steps, seven isolated intermediates, 11% overall yield from 5-chlorosalicylic acid (**2**)). In order to prepare for commercial-scale production, chemical development efforts focused on the selection of appropriate reagents and solvents for commercial-scale manufacture, refinements to reaction conditions that would lead to minimum process cycle times, and improvements in the process workups that would minimize intermediate isolations while maintaining or improving product quality. Additionally, efforts focused on the development of a commercially-viable process for the manufacture of tropinone (**7**). This was deemed important to ensure an adequate supply and a consistent quality of this key intermediate. The results of our development efforts are detailed below.

Results and Discussion

Preparation of Benzofurancarboxylic Acid (6). In the original zatosetron synthesis (Scheme 1), the benzofuran carboxylic acid moiety was prepared in five steps from 5-chlorosalicylic acid (**2**). The key step was the [3,3]-sigmatropic rearrangement of the methallyl aryl ether **4**. The benzofuran was formed by a formic acid promoted ring closure. Subsequent basic hydrolysis of the methyl ester gave the desired carboxylic acid.

For commercial-scale production, we still desired to employ the inexpensive and readily available 5-chlorosalicylic acid; however, we wished to avoid the additional step associated with the protection of the carboxylic acid as the methyl ester and the isolation of this intermediate by vacuum distillation. Although the alkylation conditions employed in the original synthesis appeared satisfactory for commercial application with respect to the choice of base and solvent, the reaction time was lengthy (22 h). The addition of catalytic amounts of KI (5 mol %), the use of powdered K_2CO_3, and a change in solvent to DMF led to a process that afforded quantitative yields of the bis-alkylated product **9**

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[†] Summer intern participant in the Lilly Engineering Education Development Program.

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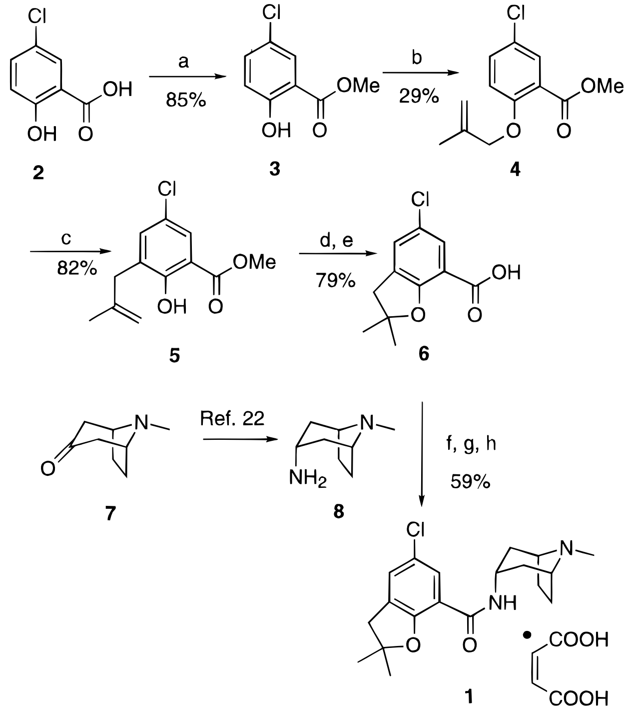
(1) (a) Cohen, M. L.; Bloomquist, W.; Gidda, J. S.; Lacefield, W. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 350−355. (b) Gidda, J. S.; Evans, D. C.; Cohen, M. L.; Wong, D. T.; Robertson, D. W.; Parli, C. J. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 695−701.

(2) (a) Robertson, D. W.; Lacefield, W. B.; Bloomquist, W.; Pfeifer, W.; Simon, R. L.; Cohen, M. L. *J. Med. Chem.* **1992**, *35*, 310−319. (b) Prous, J.; Graul, A.; Castanour, J. *Drugs Future* **1994**, *19*, 850−853.

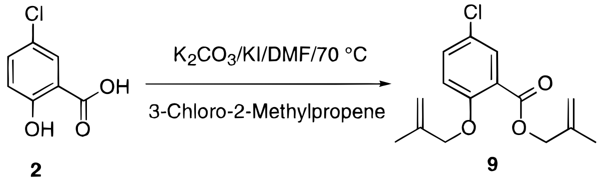
S1083-6160(97)00101-1 CCC: $14.00

Scheme 1[a]



[a] (a) MeOH, HCl; (b) 3-chloro-2-methylpropene, K_2CO_3, acetone, reflux; (c) NMP, reflux; (d) formic acid, reflux; (e) NaOH, H_2O; (f) $SOCl_2$; (g) **8**, toluene, reflux; (h) maleic acid, EtOH, ether.

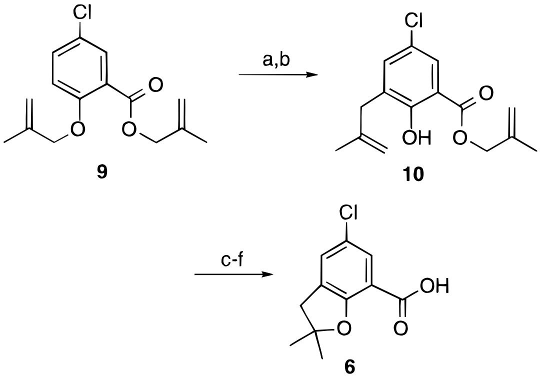
within 4−5 h at 70 °C (eq 1).



(1)

Under the above conditions, alkylation of the carboxylic acid is faster than alkylation of the phenol. Therefore, use of the bis-alkylated product **9** in the subsequent chemistries had to be addressed. If the Claisen rearrangement of **9** could be effected in yields comparable to those obtained with methyl ester **3**, then a basic hydrolysis similar to that employed in the original synthesis could be used to secure the desired carboxylic acid. Alternatively, if the Claisen rearrangement could be effected on the carboxylic acid derived from **9**, then consideration could be given to hydrolysis of the ester prior to Claisen rearrangement. Although this bis-alkylation approach does not afford optimal atom economy, the cost of the additional 3-chloro-2-methylpropene is offset by the elimination of the additional processing involved in the preparation and purification of the methyl ester. Subsequent development studies led to two approaches for transformation of **9** into the desired benzofurancarboxylic acid **6**.

Scheme 2[a]



[a] (a) Distill toluene; (b) 190 °C, 21.5 h; (c) 90% formic acid, reflux, 26 h; (d) solvent exchange; (e) concentration; (f) crystallization, toluene.

The first approach takes advantage of the lability of the methallyl ester group to the conditions of refluxing formic acid that are employed for ring closure.[3] The sequence of steps leading to **6** from **9** is shown in Scheme 2. The bis-alkylation product **9** is extracted into toluene during the workup of the alkylation reaction. This solution is concentrated to an oil by distillation at atmospheric pressure and then heated to 195 °C and held for 16 h. The rearrangement product **10** is obtained in a yield comparable to that of the original synthesis. This approach avoids the use of the costly solvent, *N*-methylpyrrolidinone, and the need for an extractive workup to isolate the product for the subsequent ring closure. Finally, the ring closure and allyl ester deprotection are effected upon refluxing in 90% formic acid for 26 h. The product is crystallized from toluene following a solvent exchange by azeotropic distillation. The overall yield across this sequence of steps is 60%, and the product is >99% pure.

The high temperature required for the rearrangement of the methallyl aryl ether **9**[4] prompted additional studies of the Claisen rearrangement step that focused on the development of milder reaction conditions for this transformation. The system under study appeared potentially suited to take advantage of the reported acceleration of the Claisen rearrangement by aqueous solvent.[5] Subsequent studies led to development of the alternative synthesis of **6**, which is outlined in Scheme 3.

Following bis-alkylation, a toluene solution of **9** is again concentrated, and then an aqueous NaOH solution, which contains 5−15 mol % of tetrabutylammonium hydrogen sulfate, is added. The mixture is refluxed with azeotropic removal of toluene until ester hydrolysis is complete. The resulting homogeneous solution is heated in a sealed reactor (~102 psig) at 170 °C for 5.5 h to effect the Claisen rearrangement. Upon acidification with concd HCl and refluxing for 6 h, ring closure is accomplished. The product is extracted into toluene and crystallized as before to afford a 75% yield of **6**, which is >99% pure.

This alternative to the synthesis of **6** offers several potential advantages over the synthesis shown in Scheme 2. The Claisen rearrangement can be effected at a lower reaction temperature in a shorter time. The ring closure can be effected with mineral acid in a shorter reaction time than the ring closure and ester deprotection sequence in 90% formic acid. This change also leads to a reduction in the product isolation time. The reduction in cycle time that is

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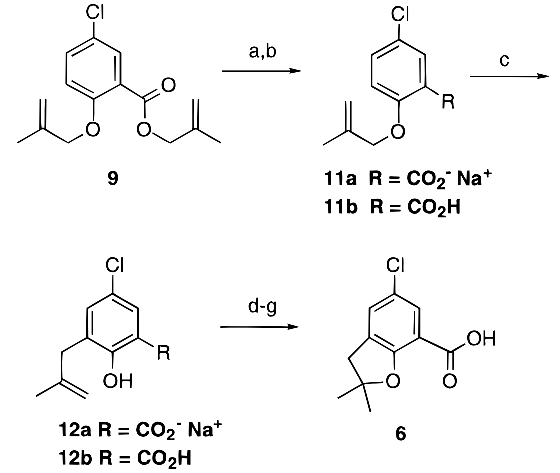
(3) Schmid, C. R. *Tetrahedron Lett.* **1992**, *33*, 757−760.

(4) Safety concerns that arise when a reactant is heated for an extended period at high temperature, as in the case of this Claisen rearrangement, were addressed through accelerated rate calorimetry studies. No evidence was seen for potentially uncontrollable exotherms.

(5) (a) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 3585. (b) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 2196−2199. (c) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515−516.

Scheme 3[a]



[a] (a) Distill toluene; (b) H_2O, *n*-Bu_4NHSO_4, NaOH, reflux ~3 h; (c) 170 °C, 5.5 h; (d) 2.7 N HCl, reflux 6 h; (e) extract with toluene; (f) concentration; (g) crystallization, toluene.

Table 1. **First-order rate constants for the Claisen rearrangement of methallyl ester 9 and sodium carboxylate 11a**

allyl ester **9**		sodium carboxylate **11a**	
temp (°C)	10^6k (s^{-1})	temp (°C)	10^6k (s^{-1})
155 (calcd)	2.1	155	83
		170	250
175	16	175 (calcd)	358
		185	712
190	55		
205	256		

realized by the replacement of formic acid with mineral acid more than offsets the additional time required to effect ester hydrolysis. In addition to the process cycle time reduction, some overall yield improvement is also noted.

In order to better define the temperature and time relationship for the Claisen rearrangements, the first-order rate constants for the Claisen rearrangements of methallyl ester **9** and an aqueous solution of **11a** were each determined at three temperatures over a 30 °C range. The results are shown in Table 1. The corresponding Arrhenius equations were derived from this data, and they were used to produce the graphical comparison of the two Claisen process options that is shown in Figure 1.[6] The contrast in reaction temperature and time for the two Claisen rearrangements is clearly evident from this graph. In addition, the sensitivity of the reaction time to temperature variation is apparent.

The above analysis is not a complete description of either Claisen rearrangement process, since it looks at only the disappearance of the starting material. A more complete kinetic analysis is complicated by two side reactions that have been identified. During the study of the Claisen rearrangement of **11a** in aqueous solution, the appearance of a secondary product, which increases in concentration relative to the primary product upon prolonged heating, is observed. Upon heating at 170 °C for 33 h, a 19:1 mixture[7] of **13b**/**12b** (Scheme 4) is obtained. The rate of this double-bond isomerization is influenced by the solution pH. Higher pH leads to more rapid isomerization. Upon reexamination, this double-bond isomerization is also noted in the Claisen rearrangement of **9**.

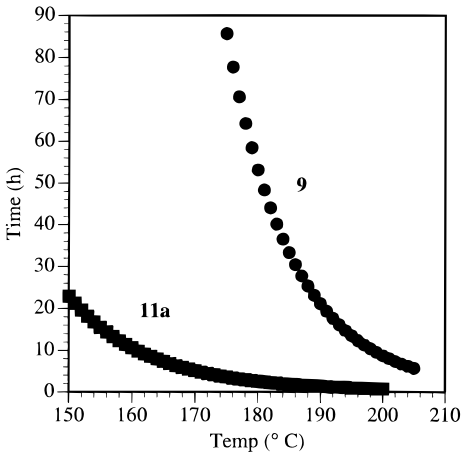
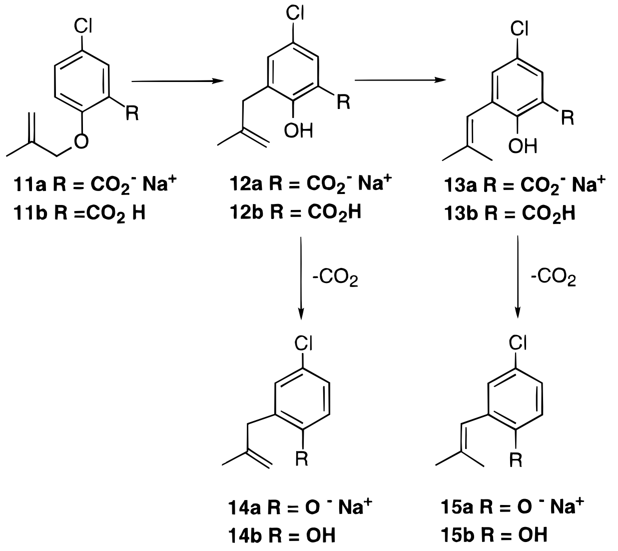


Figure 1. **Plot of the time to achieve 99% conversion of ester 9 and carboxylate 11a as a function of temperature.**

Scheme 4



Another side reaction during the Claisen rearrangement of **11a** is decarboxylation. The influence of substituents on the rate of decarboxylation of substituted salicylic acids has been studied in some detail.[8] Fortunately, the activation energy for decarboxylation of **11a** and/or **12a** is considerably higher than the activation energy for the desired Claisen rearrangement. Thus, this side reaction can be minimized by careful attention to the reaction time and temperature.[9] The minor amounts of the phenols **14b** and **15b**, which do arise during the Claisen rearrangement, are easily separated from the desired product by extraction of the aqueous reaction solution with toluene.

In their study of solvent effects on the Claisen rearrangement, White and Wolfarth[5a] report the use of a 28.5% EtOH/water mixture. Since numerous reports about acceleration of the Claisen rearrangement by acid catalysts can be found

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(6) This graph is for the time at a specified temperature required to achieve 99% conversion of the starting material.

(7) Determined by ^1H NMR integration.

(8) Dunn, G. E.; Janzen, E. G.; Rodewald, W. *Can. J. Chem.* **1968**, *46*, 2905–2909.

(9) We have not performed a kinetic analysis of the decarboxylation of **12** or **13** at this time.

Scheme 5

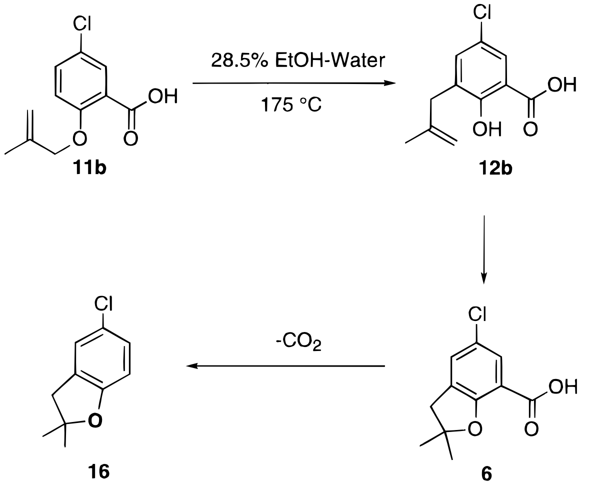

***Table 2.* Experimental design process variables and responses for a screening study of the saponification of 9**

				yield (%)	
entry[a]	concn (M)	Bu_4NHSO_4 mol %	NaOH (equiv)	**11b**[b]	**6**[c]
1	0.5	2.5	1.05	62	54
2	0.5	2.5	2.05	93	64
3	0.5	7.5	1.05	62	45
4	0.5	7.5	2.05	94	66
5	1.5	2.5	1.05	66	54
6	1.5	2.5	2.05	94	66
7	1.5	7.5	1.05	63	46
8	1.5	7.5	2.05	93	66
9	1.0	5.0	1.55	92	76
10	1.0	5.0	1.55	92	74
11	1.0	5.0	1.55	95	75

[a] The experiments were performed in a randomized order. [b] Yields were determined by HPLC analysis of a solution of **11b** versus an external reference standard. [c] Potency-corrected yield of crystalline **6**. The potency of **6** was ≥99% for all experimental runs except entry 3, for which the potency was 98%.

in the literature,[10] we have examined the rearrangement of **11b** in alcohol/water mixtures in hopes of further facilitating the desired Claisen rearrangement. Upon heating a 0.04 M solution of **11b** in 28.5% EtOH/water at 175 °C, rapid disappearance of the starting material is observed with subsequent conversion of the primary rearrangement product to the ring-closed benzofuran **6**. Under these conditions, however, this product is unstable and undergoes decarboxylation (Scheme 5). Similar reaction behavior is exhibited upon heating **11b** at 175 °C in 35% isopropyl alcohol (IPA)/water and 35% *t*-BuOH/water mixtures. Preliminary assessment of the rate of disappearance of the starting methallyl aryl ether suggests a modest rate acceleration when compared with the rearrangement of **11a** in water. When a solution of **11b** is heated in 35% IPA/water for 7 h at 135 °C, a 40% yield of crystalline **6** (~99% potency) is obtained after a workup procedure that employs an aqueous $NaHCO_3$ extraction to separate the desired carboxylic acid from the decarboxylation byproducts. We are continuing to investigate avenues to improve the selectivity for this direct conversion of **11** to **6**.

Ideally, for commercial-scale operation, the Claisen rearrangement of **11** directly follows the saponification of **9** by simple heating of the resulting carboxylate solution to the desired temperature in a closed reaction vessel. Therefore, any potential effects of the base and phase-transfer catalyst stoichiometries chosen for the saponification reaction upon the subsequent Claisen rearrangement and ring closure have to be considered. In addition, an understanding of any limitations that a practical range of concentrations for the saponification might have on this process step is needed.

A fractional factorial experimental design study has been employed to evaluate these three process variables.[11] Each experiment comprises a complete sequence of reactions from saponification to isolation of the benzofurancarboxylic acid **6**. The experimental design and the responses that were analyzed are shown in Table 2. The center point replicates (entries 9−11 in Table 2) provide a measure of the reproducibility for the reaction sequence. A comparison of the yields for the saponification step and the isolation of benzofuran shows a high degree of reproducibility. The main influence on the saponification yield arises from the variation in the base stoichiometry. At the low base stoichiometry, the saponifications do not proceed to completion within 2 h at reflux. This effect is a major contributing factor to the low benzofuran yields; however, an interaction effect between the base and phase-transfer stoichiometries is also evident. Experiments that employ a low base stoichiometry and high phase-transfer catalyst stoichiometry afford the lowest yield of the benzofuran (entries 3 and 7 in Table 2). This may be related to increased decarboxylation at the lower reaction pH, but this has not been unequivocally demonstrated. Notably, the study reveals that a fairly consistent and high quality of benzofuran can be isolated in spite of incomplete conversion in the saponification step. This indicates a good degree of process robustness.

The sequence for the synthesis of **6** shown in Scheme 3 does have some potential disadvantages. In order to perform the Claisen rearrangement in aqueous medium, the reaction vessel must be capable of handling the vapor pressure of water at the selected reaction temperature. The ring closure with mineral acid requires a fairly high acid concentration. The reaction is not homogeneous, which presents difficulties in monitoring the reaction for completion. Furthermore, as the product forms, it begins to solidify. Failure to control this at commercial scale can damage a reactor.

The problem, which is observed at laboratory scale, of uncontrolled product crystallization during the ring closure effected by aqueous mineral acid can be addressed in a number of ways. One chemical alternative, which we explored, is replacement of the mineral acid with a cation exchange resin. This necessitates selection of a suitable solvent and resin for the ring closure reaction. Four different cation exchange resins have been examined in the ring closure. Catalytic amounts (30 mol %) of Amberlyst 15, Amberlyst 36, and Amberlyst XN-1010 each afford approximately 90% conversion of a mixture of carboxylic acids **12b** and **13b** to the benzofurancarboxylic acid **6** upon

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(10) (a) Svanholm, U.; Parker, V. D. *J. Chem. Soc., Perkin Trans. 2* **1974**, 169−173. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247. (c) Ganem, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 936−945.

(11) The experimental design and analysis were facilitated by the JMP software application. JMP is a registered trademark of SAS Institute Inc.

Table 3. **Solvent screen for the formation of 6 with Amberlyst 15**

solvent	yield (%)[a]	potency of **6** (%)
CH_2Cl_2	83	>99
DCE	84	>99
toluene	66	97
heptane[b]	50	>99
EtOAc	67	>99
i-PrOAc	55	95
t-BuOEt	<4	
heptane/EtOAc (4:1)	58	96

[a] Potency-corrected yield of crystalline **6**. [b] Product crystallized during the reaction, and ethyl acetate was added to facilitate sampling and isolation.

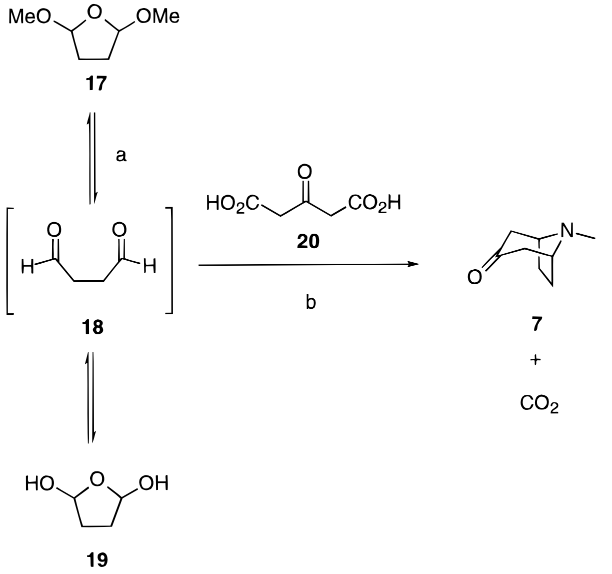
refluxing in CH_2Cl_2 within 6−8 h. Nafion NR50 affords only about 50% conversion after refluxing in CH_2Cl_2 for 6 h. Subsequent solvent selection studies have been performed with Amberlyst 15 (Table 3). The two chlorinated hydrocarbon solvents afford the best yields and good product quality upon crystallization from toluene following a solvent exchange. The other solvents result in either incomplete conversion, even after extended refluxing, or the formation of unidentified byproducts.

This method of ring closure is readily coupled with the aqueous Claisen rearrangement by extraction of the rearranged acid into either DCE or CH_2Cl_2. In this fashion, the benzofurancarboxylic acid **6** is obtained in 75% yield and >99% purity from **11b**. Thus, the two approaches to ring closure give **6** of comparable yield and quality.

Of the procedures described for the synthesis of **6**, the aqueous Claisen rearrangement coupled with the use of aqueous HCl to effect the ring closure is preferred. This approach minimizes the overall process cycle time, reduces the volume of organic solvent required for processing, and avoids the use of the halogenated hydrocarbon solvent.

Preparation of Tropinone (7). Tropinone is commercially available from natural sources. However, suppliers of tropinone could not guarantee the availability of sufficient quantities needed to support long-term production of zatosetron. For this reason, an economical preparation of **7** was pursued. Since its identification as a central component of the atropine alkaloids, a number of routes have been developed to prepare **7**. Tropinone was first prepared in 1896 by the oxidation of tropine.[12] The well-known three-component coupling of butanedial (**18**), acetone-1,3-dicarboxylic acid (**20**), and $MeNH_2$ reported by Robinson constituted the first synthesis of tropinone, providing the compound in 42% yield.[13] Tropinone has also been prepared by the addition of $MeNH_2$ to cycloheptadienone.[14] A drawback to the development of this preparation is that cycloheptadienone is commercially unavailable and requires a minimum of two steps from cycloheptanone.[15] More recently, tropinone has been prepared by the $Fe_2(CO)_6$-catalyzed addition of 1,1,3,3-tetrabromoacetone with carbomethoxypyrrole.[16] The expense and toxicity of the reagents preclude consideration of this route for the manufacture of **7**. Optimization of the Robinson synthesis provided the most economical manufacturing route to tropinone.

Scheme 6 [a]



[a] (a) H_2O, HCl (0.1 equiv), 95 °C; (b) H_2O, $MeNH_2$·HCl (2 equiv), NaOAc, pH 5, 55−60 °C.

In the Robinson synthesis, butanedial dioxime was utilized as a precursor to the unstable dialdehyde (**18**), and the acetonedicarboxylic acid was neutralized with $CaCO_3$. A modification to this process includes the use of 2,5-dimethoxytetrahydofuran (DMTHF, **17**) as a precursor to the dialdehyde and pH control of the reaction using a buffer solution. Elming[17] reported the acid-catalyzed hydrolysis/Mannich reaction outlined in Scheme 6. Hydrolysis of DMTHF (**17**) at 95 °C for 30 min provided an aqueous solution of **18**.[18] After cooling, the dialdehyde-containing solution was neutralized and added to a mixture of **20** (2 equiv) and $MeNH_2$·HCl (2 equiv) in water buffered to pH 5 with NaOAc. The mixture was heated, and CO_2 was liberated. Addition of K_2CO_3 and NaCl, then isolation by extraction, drying, and distillation gave an 81% yield of **7**. In our hands, this procedure gave 50−60% yields of **7** with decomposition on distillation. Hydrolysis conditions, pH, temperature, stoichiometry, isolation, and alternate raw material sources were studied in our development of a commercial-scale process to prepare **7**.[19]

The aqueous acid hydrolysis of DMTHF forms lactol **19** as indicated by GC analysis. With a pH 5 buffer solution at 80 °C for 1 h, no hydrolysis is observed. At pH 1, a minimum temperature of 65 °C is necessary for complete

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(12) Willstater, R. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 393−407.

(13) (a) Robinson, R. *J. Chem. Soc.* **1917**, 762−768. (b) Schopf, C.; Lehman, G. *Justus Liebigs Ann. Chem.* **1935**, *518*, 1−23.

(14) (a) Bottini, A. T.; Gal, J. *J. Org. Chem.* **1971**, *36*, 1718−1719. (b) Sato, T.; Sato, K.; Mukai, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1708−1709. (c) Kashman, Y.; Cherkoez, S. *Synthesis* **1974**, 885−887.

(15) (a) MacDonald, T. L.; Dolan, R. *J. Org. Chem.* **1979**, *44*, 4973−4976. (b) Krabbenhoft, H. O. *J. Org. Chem.* **1979**, *44*, 4285−4294. (c) Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109−2120.

(16) Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1786−1791.

(17) Elming, N. In *Advances in Organic Chemistry*; Raphael, R. A., Taylor, E. C., Wynberg, H., Eds.; Interscience: New York, 1960; Vol. 2, pp 67−115.

(18) Attempts to monitor the reaction by ^{13}C NMR gave no indication that aldehyde was present in the reaction mixture. Signals as high as 106 ppm were observed (carbinol carbons). No resonances were observed further downfield.

(19) Any change in the order of addition of reagents resulted in reduced yields of tropinone.

hydrolysis of DMTHF to the lactol **19** in 30 min. Hydrochloric acid gives better yields of tropinone than sulfuric acid.

At pH ≤ 4, the dicarboxylic acid (**20**) decarboxylates, resulting in reduced yields of **7**. At pH ≥ 6, the reaction is slow, and yields are also depressed. As decarboxylation occurs, the reaction pH increases. In fact, at pH 2.5 the yield of **7** is 50%, while at pH 8.5 the yield is 30%. We employed sufficient buffer (NaOAc, 4 equiv) in the reaction to maintain an optimal pH range (pH 4.0−6.0) throughout the reaction to obtain **7** in 75−85% yield.

The diacid **20** decarboxylates at elevated temperatures (above 40 °C). For process control, it is preferred that the condensation reaction and the corresponding decarboxylation occur as the lactol (**19**) is combined with the diacid/amine solution. Addition of the lactol solution at 12−15 °C results in immediate CO_2 evolution and is easily controlled. Below 10 °C, the reaction is slow and no decarboxylation of the Mannich intermediate is observed. Extended dialdehyde solution addition times do not reduce the yield.

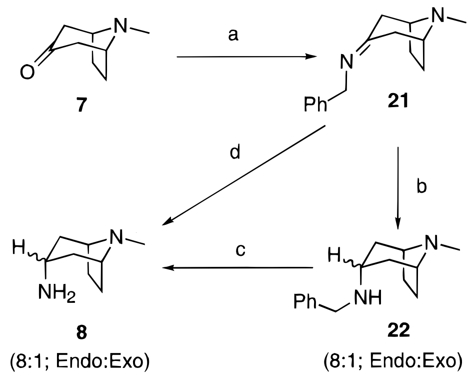
As the diacid **20** is the most expensive component of the process, we have carried out the procedure using 1.1 equiv each of **20** and $MeNH_2$, relative to **17**. The crude tropinone yield is not affected by the reduced stoichiometry, as long as careful pH control is maintained.

The $MeNH_2 \cdot HCl$ can be replaced as a reagent with a 40% aqueous $MeNH_2$ solution provided that the solution is neutralized with 1 equiv of acid. A pH 5 solution is obtained when 1 equiv of concd HCl is added to the reaction mixture prior to the aldehyde addition. Once again, the optimal pH 5−6 is maintained throughout the reaction by the NaOAc buffer.

Additional cost savings were realized when a supplier of a 40% aqueous solution of **18** was identified.[20] Use of this source of **18** replaces DMTHF as a reagent and eliminates the need for the acid hydrolysis step. The modified process gives tropinone in greater than 90% yield. Using aqueous **18** reduces the process to a one-pot procedure.

Crude tropinone produced by the above procedure is isolated by concentration as an orange oil, which solidifies on standing. This material is 90−95% pure by GC analysis. Due to its low melting point (mp 40−42 °C) and high solubility in organic solvents, isolation as a crystalline solid results in significant yield loss. Isolation by distillation has been carried out on a small scale (bp 76−78 °C (0.6 mmHg)) and is accompanied by decomposition. Use of the crude tropinone in downstream processing has been demonstrated as a viable alternative to purification by crystallization or distillation.[21]

Scheme 7 [a]



[a] (a) $BnNH_2$, toluene, azeotrope; (b) PtO_2, H_2, EtOH; (c) Pd/C, H_2, EtOH; (d) 2% Pt and 8% Pd on carbon, H_2; EtOH.

Preparation of 3-*endo*-Tropanamine (8). The published method for preparing *endo*-tropanamine (**8**) relies on the catalytic hydrogenation (PtO_2, EtOH, H_2) of the Schiff base **21** derived from tropinone (**7**) and benzylamine to introduce the endo amine functionality.[22] Subsequent removal of the benzyl group from **22** by catalytic hydrogenolysis (Pd/C, EtOH, H_2) yields **8** (Scheme 7). The imine hydrogenation and hydrogenolysis of the benzyl group can be carried out in a single reaction vessel utilizing a 2% Pt/8% Pd/C catalyst (Scheme 7).[23] This route has been used to prepare **8** on a pilot scale (300 gal). In practice, this method requires high catalyst quantities (50% catalyst by weight) to insure complete reduction of the imine and removal of the benzyl protecting group. The resulting tropanamine product contains various impurities due to incomplete Schiff base formation or decomposition of the imine during reduction. This hydrogenation approach yields an 8:1 mixture of *endo*- to *exo*-tropanamine, which is difficult to separate.[24] The modest selectivity of the imine reduction, the difficulties in reproducibly preparing the Schiff base, and the high catalyst loads required for its reduction led us to seek further improvements for the tropanamine manufacture. It is known that sterically bulky reducing agents provide a method of reducing cyclohexanimines that preferentially gives axial amine products with high stereoselectivity.[25,26] Reduction of the Schiff base **21** with DIBAL provides good yields of the *N*-benzyltropanamine (**22**) in slightly better stereoselectivity (9:1 endo:exo).[27] However, from a manufacturing standpoint, this method would require cryogenic cooling and disposition of an undesired aluminum waste stream. In addition, we desired to avoid the generation and isolation of the unstable imine, **21**.

A logical approach to the preparation of **8** is through a one-step reductive amination procedure. Reductive amina-

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(20) Butanedial is available as a 40% aqueous solution from Chemie Linz North America Inc., 65 Challanger Rd., Ridgefield Park, NJ 07660.

(21) Tropinone can be isolated by sublimation, but this is not a viable option for large-scale production. It can also be isolated by crystallization as the hydrochloride salt; however, this method of isolation results in significantly reduced yields (<50%).

(22) (a) Archer, S.; Lewis, T. R.; Unser, M. J. *J. Am. Chem. Soc.* **1957**, *79*, 4194−4198. (b) Bagley, J. R.; Riley, T. N. *J. Heterocycl. Chem.* **1977**, *14*, 599−602.

(23) The 2%Pt/8% Pd on carbon catalyst is available from Engelhard Chemical Catalyst R and D, 23800 Merchantile Road, Beachwood, OH, 44122.

(24) Removal of the undesired exo isomer can be achieved by acylation with the requisite acid chloride and recrystallization of the zatosetron maleate salt; however, this results in an inefficient use of the benzofuran intermediate.

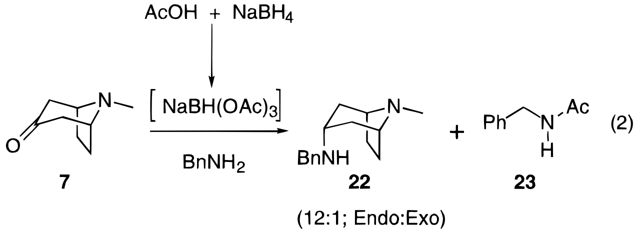
(25) (a) Wrobel, J. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 3447−3450. (b) Hutchins, R. O.; Su, W.-Y. *Tetrahedron Lett.* **1984**, *25*, 695−698. (c) Hutchins, R. O.; Rutledge, M. C. *Tetrahedron Lett.* **1987**, *28*, 5619−5622. (d) For a review on the reduction of imines, see: Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, pp 25−78. (e) For a review of diastereoselective and enantioselective reduction of imines, see: Zhu, Q.-C.; Hutchins, R. O.; Hutchins, M. K. *Org. Prep. Proced. Int.* **1994**, *26*, 193−236.

(26) Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412−3422.

(27) Gregory, J. A.; Jennings, A. J.; Joiner, G. F.; King, F. D.; Rahman, S. K. *Tetrahedron Lett.* **1995**, *36*, 155−158. The authors of the referenced paper reported that the reduction of tropinone oxime with alane provides exclusively the endo amine product; however, no experimental data are provided.

tions using the common Borch conditions ($NaBH_3CN$)[28] or borohydride exchange resin (BER)[29] have been described as convenient methods for introducing the amine functionality without prior formation of the Schiff base. Unfortunately, reductive amination of **7** by the action of $NaCNBH_3$ or BER gives only slight preference to the endo amine product (2:1 endo:exo).[30,31] Recently, Abdel-Magid introduced sodium triacetoxyborohydride [$NaBH(OAc)_3$] as a mild hydride source, which is equally effective in the reductive amination of ketones.[32] This report, combined with the observation that the reduction of imines derived from various substituted cyclohexanones with sodium borohydride in acetic acid (presumably by $NaBH(OAc)_3$) shows preferential attack of hydride from the equatorial face,[26] made this an attractive option to explore for the commercial-scale production of tropanamine.

Using the general procedure reported by Abdel-Magid,[32a] the reductive amination of tropinone (1 equiv) and benzylamine (1.1 equiv) with $NaBH(OAc)_3$ (1.5 equiv) and acetic acid (1.0 equiv) in 1,2-dichloroethane (DCE) produces a 12:1 mixture of predominately *endo*-*N*-benzyltropanamine (eq 2).[30,33] Although this procedure gives a lower number of impurities, a substantial quantity of *N*-benzylacetamide, **23** (15−20%), is observed in the reaction mixture. Presumably, this byproduct is formed by the addition of benzylamine to the acetoxyborohydride.[34] This has been verified by reacting $NaBH(OAc)_3$ and benzylamine in the absence of tropinone.



The $NaBH(OAc)_3$ reductive amination has been examined in several different solvents including CH_2Cl_2, DCE, $CHCl_3$, THF, ACN, toluene, EtOAc, and DME. The solvents have been evaluated by comparing the yield of benzyltropanamine, the endo:exo ratio of benzyltropanamine, the percentage of *N*-benzylacetamide, and the amount of unknown impurities. Dichloromethane proves to be the best solvent for this reductive amination. Reactions in CH_2Cl_2 show complete conversion of tropinone to the benzyltropanamine in high yields, with the highest endo:exo ratios, the lowest levels of benzylacetamide (2−4%), and no significant unknown impurities.

Table 4. **Experimental design process variables and responses for a screening study of the reductive amination of tropinone**

entry[a]	$NaBH(OAc)_3$ (equiv)	benzylamine (equiv)	AcOH (equiv)	endo:exo ratio[b]	amount of **23** (%)
1	1.0	1.2	0.5	16:1	3.6
2	1.0	1.2	1.5	14:1	2.6
3	1.0	1.8	0.5	15:1	6.0
4	1.0	1.8	1.5	13:1	4.8
5	1.5	1.5	1.0	16:1	7.2
6	1.5	1.5	1.0	16:1	7.1
7	1.5	1.5	1.0	15:1	8.8
8	2.0	1.2	0.5	20:1	6.2
9	2.0	1.2	1.5	13:1	7.9
10	2.0	1.8	0.5	18:1	19.4
11	2.0	1.8	1.5	15:1	10.7

[a] The experiments were performed in a randomized order. [b] Ratios were determined by GC analysis of the crude reaction mixtures. See ref 30.

The effects of stoichiometry for the $NaBH(OAc)_3$ preparation of **22** have been evaluated using statistically designed experiments.[35] The experimental design and the responses that were analyzed are shown in Table 4. Increased amounts of hydride are required to drive the reaction to completion, and increased amounts of benzylamine are necessary because of the loss of the reagent to benzylacetamide formation. The lowest levels of **23** are found at low stoichiometries of hydride and benzylamine. The amount of acetic acid does not have a significant effect on the yield. However, the additional acetic acid does accelerate the reaction rate.[36] The highest endo:exo ratio of **22** is achieved at the low level of acetic acid and the high level of hydride. These experiments have led us to a standard stoichiometry of 1.5 equiv of $NaBH(OAc)_3$, 1.35 equiv of benzylamine, and 0.75 equiv of acetic acid.

While commercial quantities of $NaBH(OAc)_3$ may be obtained, the purchase of $NaBH(OAc)_3$ is expensive when compared to the cost of $NaBH_4$ and acetic acid. In addition, we have observed large discrepancies in the results of experiments that used different lots of solid $NaBH(OAc)_3$. In order to reduce the cost of the reagent and increase the robustness of the process with respect to the hydride source, in situ generated $NaBH(OAc)_3$ has been employed. Sodium triacetoxyborohydride was easily prepared in situ by the slow addition of acetic acid (3.5 equiv relative to $NaBH_4$) to a slurry of $NaBH_4$ (1.5 equiv relative to tropinone) in CH_2Cl_2.[37] The reaction mixture is stirred at room temperature and is monitored for completion by the evolution of hydrogen

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(28) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897−2904. (b) Lane, C. F. *Synthesis* **1975**, 135−146.

(29) Yoon, N. M.; Kim, E. G.; Son, H. S.; Choi, J. *Synth. Commun.* **1993**, *23*, 1595−1599.

(30) The endo:exo ratio is measured by GC analysis of the crude reaction mixtures. Conditions for the GC assay are provided in the Experimental Section.

(31) This result is consistent with the results in ref 26, which demonstrated that reductions of 4-substituted cyclohexanone imines with $NaBH_4$ and $NaBCNH_3$ preferentially favor attack via an axial hydride delivery.

(32) (a) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595−5598. (b) Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett* **1990**, 537−539. (c) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862. (d) Abdel-Magid, A. F.; Maryanoff, C. A. *ACS Symp. Ser.* **1996**, *641*, 201−216.

(33) Reference 32c reports a 20:1 ratio (endo:exo, as determined by ^1H NMR integration) of *N*-benzyltropanamine produced by identical reaction conditions. We found that the GC assay described in the Experimental Section provides a more precise measurement of the endo:exo ratio.

(34) (a) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F. M. *J. Org. Chem.* **1975**, *40*, 3453−3456. (b) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766−768.

(35) The variables and ranges used in a factorial design (low, mid, high) were as follows: benzylamine (1.2, 1.5, 1.8 equiv); $NaBH(OAc)_3$ (1.0, 1.5, 2.0 equiv); and acetic acid (0.5, 1.0, 1.5 equiv). The equivalents were measured relative to the amount of tropinone. The measured responses included the yield of benzyltropanamine, the *endo*- to *exo*-benzyltropanamine ratio, the amount of benzylacetamide impurity, and the amount of residual tropinone.

(36) In the reaction with added acetic acid, the reaction was 90% complete within 7 h, whereas, without acetic acid added, there was 15% tropinone remaining even after 30 h.

(37) The $NaBH(OAc)_3$ reagent is not completely soluble in CH_2Cl_2; therefore, the reaction mixture is a heterogeneous slurry.

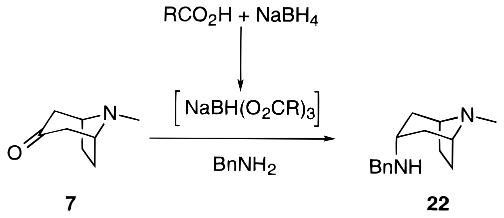
Table 5. **Ratio of *endo*- to *exo-N*-benzyltropanamine (22) from the reductive amination of 7 using (acyloxy)borohydrides derived from various carboxylic acids in CH_2Cl_2**

entry	carboxylic acid (RCOOH)	endo:exo ratio[a]
1	acetic acid	12:1
2	propionic acid	14:1
3	isobutyric acid	16:1
4	pivalic acid	15:1
5	butyric acid	14:1
6	valeric acid	13:1
7	hexanoic acid	14:1
8	cyclohexanecarboxylic acid	8:1
9	2-ethylbutyric acid	30:1
10	2-ethylhexanoic acid	>50:1
11	$NaBH_3CN$ or BER	2:1

[a] Ratios determined by GC analysis of the crude reaction mixtures. See ref 30.

gas. After the evolution of hydrogen gas has stopped (generally 3−4 h after addition of acetic acid), the reductive amination is performed by addition of tropinone and benzylamine. Using the in situ generated $NaBH(OAc)_3$, the reductive amination reaction performed with the above stoichiometry gives complete conversion of tropinone within 18 h and produces only 2−4% of the *N*-benzylacetamide impurity. At the completion of the reaction the excess reagent is quenched by the slow addition of aqueous NaOH (5 N). The aqueous hydroxide wash also separates the acetic acid from the product. The benzyltropanamine product (12:1 endo:exo) can be isolated by concentration of the CH_2Cl_2 layer; however, the crude product is sufficiently pure for hydrogenolysis of the benzyl group without further purification.

In an effort to further increase the selectivity for the endo isomer, we explored the use of different (acyloxy)borohydrides prepared from $NaBH_4$ and various carboxylic acids of increasing steric bulk (eq 3).[38] The hydride reagents are

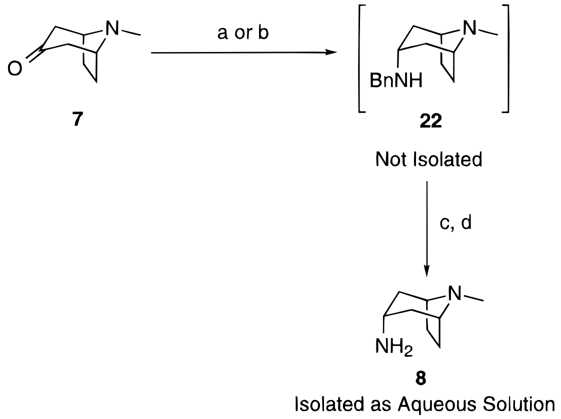


(3)

prepared in situ by the addition of 3.5 equiv of the carboxylic acid to $NaBH_4$ and used directly in the reductive amination of tropinone (eq 3).[39,40] The endo:exo ratio of benzyltropanamine isomers observed in the reductions with the different reagents is given in Table 5.

As anticipated, the selectivity for the axial amine product is enhanced by increasing the steric bulk of the carboxylic acid moiety of the (acyloxy)borohydride reagent. The hydride reagents derived from 2-ethylbutyric acid (entry 9) and 2-ethylhexanoic acid (entry 10) show a dramatic improvement in the stereoselectivity for 3-*endo-N*-benzyltropanamine. Besides the enhanced stereoselectivity, the reagents derived from 2-ethylbutyric or 2-ethylhexanoic acid have several distinct advantages over $NaBH(OAc)_3$. They are completely soluble in CH_2Cl_2. The homogeneous reactions are readily stirred and easily sampled. Most of the other hydride reagents (see Table 4), including $NaBH(OAc)_3$, form thick slurries or gelatinous reaction mixtures. Additionally, unlike reductions with $NaBH(OAc)_3$, reactions with tris[(2-ethylbutanoyl)oxy]borohydride or tris[(2-ethylhexanoyl)oxy]borohydride[41] show none of the corresponding *N*-benzyl amide impurity. However, the rate of the reactions with these hydride reagents is much slower. In the reactions with tris[(2-ethylhexanoyl)oxy]borohydride, the buildup of the concentration of the intermediate imine **21** in the reaction indicates that hydride reduction is rate limiting. In order for the imine intermediate to be completely consumed in a reaction time similar to that of the $NaBH(OAc)_3$ reactions, 2 equiv of the tris[(2-ethylhexanoyl)oxy]borohydride reagent is employed. The increased stoichiometry requires the use of greater quantities of 2-ethylhexanoic acid; however, this acid may be recovered from the NaOH wash. The stereoselectivity benefit realized in the reactions with tris[(2-ethylhexanoyl)oxy]borohydride translates to a more efficient use of the benzofurancarboxylic acid **6** in the production of zatosetron because the undesired exo isomer no longer has to be discarded.

Scheme 8 [a]



[a] (a) $NaBH(OAc)_3$, ($NaBH_4$ + AcOH), $BnNH_2$, CH_2Cl_2; (b) $NaBH(O_2CR)_3$, ($NaBH_4$ + 2-ethylhexanoic acid), $BnNH_2$, CH_2Cl_2; (c) wash 5 M NaOH, extract into H_2O, 2 M HCl; (d) 5% Pd/C, H_2, H_2O, pH 9.0.

Deprotection of the benzyl-protected amine **22** is achieved by hydrogenolysis (H_2, 5% Pd/C, 50 psig, 70 °C) in EtOH or IPA (Scheme 8). The hydrogenolysis in EtOH is complicated by the formation of *N*-ethyltropanamine. In either solvent, tropanamine is isolated as a crude oil contaminated with benzylacetamide by concentration of the reaction mixture after the filtration of the catalyst. In order to avoid the undesired concentration steps, we chose to extract the benzyltropanamine from the CH_2Cl_2 solution with aqueous HCl (2 M) and perform the hydrogenolysis (H_2, 5%

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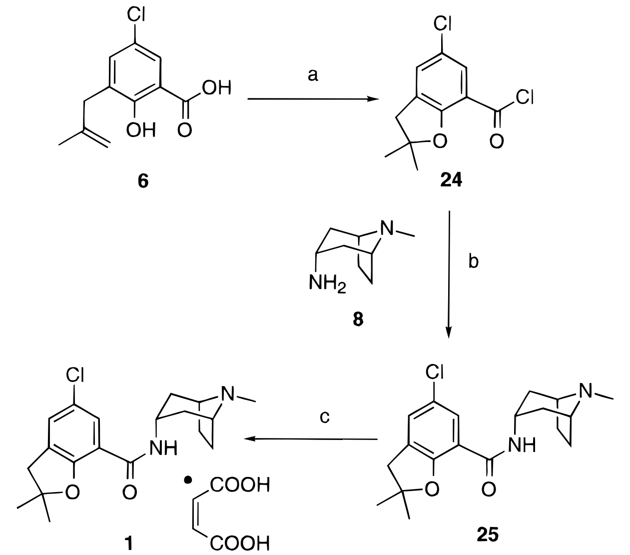
(38) McGill, J. M.; LaBell, E. S.; Williams, M. *Tetrahedron Lett.* **1996**, *37*, 3977−3980.

(39) The preparation of various (acyloxy)borohydrides has been described previously. For example, see: Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535−536. For a review of (acyloxy)-borohydrides, see: (a) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317−384. (b) Gribble, G. W. *ACS Symp. Ser.* **1996**, *641*, 166−200.

(40) Because the reagents are prepared in situ, the exact reducing species is not known and therefore may be a mixture of substituted (acyloxy)borohydride species.

(41) The reagent prepared from (±)-ethylhexanoic acid should also be a mixture of diastereomers.

Scheme 9[a]



[a] (a) $SOCl_2$, cat. DMF, toluene; (b) **8** (aqueous solution), toluene, pH ≥7.5; (c) maleic acid, EtOH, EtOAc, recrystallization.

Pd/C, 50 PSI, 70 °C) in an aqueous medium (Scheme 8). The aqueous extraction leaves the *N*-benzyl amide impurity in the discarded CH_2Cl_2 layer. The cleavage of the benzyl group from **22** is not pH dependent, but the residual benzylamine extracted into the aqueous layer is hydrogenolyzed only if the reaction pH is above 9. This aqueous hydrogenolysis procedure yields a very pure aqueous solution of **8** that is suitable for use in a subsequent amidation to produce zatosetron. Tropanamine may also be isolated from the hydrogenolysis as a crude oil or as a dihydrochloride salt. To avoid the solvent concentrations necessary for the isolation of the crude oil and the yield loss associated with dihydrochloride salt formation, we chose to not isolate **8** but to use the aqueous solution directly in a Schotten−Baumann acylation of **24** (see below).

Synthesis of Zatosetron Maleate (1). In the original synthesis of zatosetron the acylation was carried out in toluene, necessitating the isolation of both the acid chloride **24** and tropanamine (**8**) prior to the reaction. The zatosetron free base (**25**) precipitated from solution as it formed, yielding a thick slurry, which made isolation difficult. Therefore, we adopted a strategy to perform the amidation under Schotten−Baumann conditions (toluene/water) (Scheme 9).

First the carboxylic acid **6** is converted to the acid chloride **24** by the action of $SOCl_2$ (1.2 equiv) in the presence of a catalytic amount of DMF (3 mol %). The acid chloride formation is performed in toluene (45−50 °C) and is complete in 2 h. The acid chloride is not isolated but is combined with an aqueous solution of **8** (see above) and heated to 50 °C to effect the amidation. The reaction mixture is maintained at pH ≥7.5 by the addition of 5 M NaOH. The Schotten−Baumann approach allows for the use of excess $SOCl_2$ during the formation of **24** without the excess reagent having to be removed. Upon completion of the amidation, zatosetron (**25**) is extracted from the toluene layer with aqueous HCl and the free base is precipitated from this aqueous solution by the addition of NaOH. The free base product is easily filtered from the aqueous mixture in good yield (88%); however, there is not a significant improvement in the endo:exo ratio from the tropanamine. The maleate salt (**1**) is crystallized from EtOH/EtOAc after treatment of the free base with a slight excess of maleic acid (80%). The formation and crystallization of the maleate salt adequately removes the undesired exo isomer, yielding a high-quality bulk drug substance.

Conclusions

We have presented an efficient route for the commercial-scale manufacture of the $5HT_3$ receptor antagonist zatosetron maleate (**1**). We have demonstrated two alternative approaches to the key benzofurancarboxylic acid **6**. One approach takes advantage of the lability of an allyl ester protecting group to refluxing 90% formic acid to effect ester deprotection while simultaneously accomplishing ring closure. The second approach takes advantage of the accelerating effect of an aqueous medium on the Claisen rearrangement to allow this critical transformation to be performed at a lower temperature and in a shorter time. In addition, the alternative conditions for ester deprotection and ring closure of the latter approach offer further opportunities for cycle time reduction. This work also highlights key side reactions that are encountered in the application of the Claisen rearrangement for the preparation of benzofurans from salicylic acid derivatives. We have described improved conditions for the preparation of tropinone (**7**) in reproducibly high yields from inexpensive and readily available raw materials. Furthermore, we have demonstrated a method for the direct conversion of tropinone to *endo*-tropanamine (**8**) that employs the in situ generation of $NaBH(OAc)_3$ to give improved selectivity for the desired endo isomer. In addition, we have demonstrated the use of sodium tris[(2-ethylhexanoyl)oxy]borohydride for highly stereoselective reductive aminations. This methodology provides a simple and inexpensive alternative to the use of bulky hydride reagents and potentially has other applications in process chemistry.

Experimental Section

General Procedures. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted. Melting points were obtained on a Meltemp II apparatus, a Thomas Hoover Meltemp apparatus, or an Electrotherm 1A9300 digital apparatus and are uncorrected. ^1H NMR spectra were recorded at 300 MHz; ^{13}C NMR spectra were recorded at 75 MHz. The ratios of *endo*- to *exo*-tropanamine were obtained by capillary gas chromatography with a CAM capillary column (15 m × 0.5 m i.d.). GC measurements were performed on a Hewlett-Packard 5200 GC instrument equipped with a flame ionization detector (FID) and a Hewlett-Packard electronic integrator. The carrier gas (helium) flow rate was 1 mL/min with a 20:1 split ratio. The oven temperature was increased from 100 to 220 °C over 30 min. GC−MS analyses were performed on a VG Trio 2 quadrupole mass spectrometer with a 30-m capillary DB-1 column (0.32 mm i.d. × 0.25 μm film thickness) at an initial temperature of 100 °C for 2 min followed by a 20 °C/min ramp. HPLC analyses were performed with a Spectra Physics Model 8800 LC pump, Spectra Physics Model 4400 integrator, Kratos Spectraflow 757 absorbance detector, and Fiatron CH-30 column oven. A Micromiretics 728 autosampler was employed for sample injection with a 20-μL injection loop. Analytical HPLC was conducted on a Zorbax RX-C8 column (25 cm × 4.6 mm i.d.) with an isocratic eluent system of 0.025 M aqueous NaH_2PO_4 (pH 3.0)/CH_3CN (40:60) at a flow rate of 1 mL/min, a column temperature of 25 °C, and UV detection at 230 nm.

5-Chloro-2-[(2-methyl-2-propenyl)oxy]benzoic Acid 2-Methyl-2-propenyl Ester (9). A four-neck, 500-mL, round-bottom flask was equipped with a mechanical stirrer, condenser, N_2 vent, and thermometer with a temperature controller connected to a heating mantle. The reaction flask was charged with K_2CO_3 (35.0 g, 0.25 mol), KI (1.0 g, 0.006 mol), and DMF (50 mL). A solution of 5-chlorosalicylic acid (**2**) (20.0 g, 0.12 mol) in DMF (50 mL) was added from an addition funnel over about 5 min to the stirred reaction slurry while allowing the temperature to rise. The addition funnel was rinsed with DMF (5 mL). The stirred slurry was heated to 65−70 °C, and 3-chloro-2-methylpropene (26.9 g, 0.28 mol) was added rapidly from an addition funnel. The slurry was held at 60−70 °C for about 21 h. The reaction was essentially complete after 4.75 h and showed little change over the remaining period of heating, as determined by HPLC analysis. Heating was discontinued; toluene (100 mL) and deionized water (200 mL) were added. The mixture was stirred until all of the solids were dissolved, and then the layers were separated. The aqueous phase was extracted with additional toluene (100 mL). The combined organic phase was washed with deionized water (2 × 50 mL) and then concentrated under vacuum at a bath temperature of 50 °C to leave 33.7 g of a straw-colored liquid. The oil was >99% a single peak by HPLC analysis. ^{1}H NMR showed about 3% residual toluene.

Typically, the toluene solution of **9** is used in subsequent reactions without further purification. An analytically pure sample of **9** was obtained by fractional vacuum distillation: bp 25−28 °C (2−3 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 6 H), 4.46 (s, 2 H), 4.70 (s, 2 H), 4.94 (br s, 1 H), 4.97 (br s, 1 H), 5.05 (s, 1 H), 5.13 (s, 1 H), 6.86 (d, 1 H, $J = 8.9$ Hz), 7.35 (dd, 1 H, $J = 2.7, 8.9$ Hz), 7.77 (d, 1 H, $J = 2.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 19.2, 19.6, 68.4, 72.6, 113.1, 113.3, 114.7, 121.7, 125.2, 131.3, 132.9, 139.8, 139.9, 156.8, 164.7; IR ($CHCl_3$) 1726, 1658, 1599, 1486, 1452, 1410, 1116, 1082, 910 cm^{-1}. Anal. Calcd for $C_{15}H_{17}ClO_3$: C, 64.17; H, 6.10; Cl, 12.63. Found: C, 64.38; H, 6.08; Cl, 12.40.

Claisen Rearrangement of Allyl Ester 9 and Ring Closure with Formic Acid. A toluene solution of **9**, prepared as described above, was charged into a four-neck, 500-mL, round-bottom flask, and the solution was heated to 195 °C with removal of toluene through a Dean−Stark trap. The residue was held at 195 °C for 16 h, and after cooling to <90 °C, formic acid (90%, 75 mL) was added. This solution was heated to vigorous reflux (104−108 °C) and held for 27 h. Formic acid (~25 mL) was distilled off, and toluene (75 mL) was added. The remaining formic acid was removed by azeotropic distillation. The solution was cooled to 0 °C and stirred for 2 h. The product was filtered, washed with chilled toluene (50 mL), and dried under vacuum overnight at 40−50 °C to give 15.7 g of **6** (60%), which was >99% pure by HPLC analysis. 5-Chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acid (**6**): mp 160−162 °C (lit.[2a] mp 159−161 °C); ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 6 H), 3.03 (br s, 2 H), 7.27 (dt, 1 H, $J = 1.2, 2.3$ Hz), 7.75 (dt, 1 H, $J = 1.2, 2.3$ Hz), 11.0 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.1, 41.8, 91.3, 112.8, 125.4, 129.6, 130.5, 131.1, 157.5, 166.6; IR ($CHCl_3$) 3381, 1741, 1695, 1602, 1452, 1373 cm^{-1}. Anal. Calcd for $C_{11}H_{11}ClO_3$: C, 58.29; H, 4.89; Cl, 15.64. Found: C, 58.13; H, 4.84; Cl, 15.90.

5-Chloro-2-[(2-methyl-2-propenyl)oxy]benzoic Acid (11b). Crude ester **9** (51 g, 0.18 mol) in THF (250 mL) was combined with an aqueous NaOH solution (2.2 N, 100 mL). The stirred mixture was heated to reflux and held for 6.5 h, after which no starting material was evident by TLC analysis. The reaction mixture was cooled to ambient temperature and diluted with deionized water (450 mL) and toluene (200 mL). The layers were separated, and the aqueous layer was reextracted with toluene (200 mL). The combined organic phase was extracted with 1 N NaOH (50 mL) and brine solution (50 mL). These aqueous extracts were combined with the original aqueous phase and acidified with concd HCl (20 mL). The mixture was extracted with toluene (1 × 300 mL and 1 × 200 mL). The combined organic phase was washed with brine solution (100 mL) and dried over anhyd Na_2SO_4. After removal of the drying agent, concentration at reduced pressure left 37.2 g of a colorless oil, which began to solidify upon standing. Trituration with hexanes afforded a slurry, which was filtered and dried under vacuum to give 33.6 g (82%) of acid **11b**: mp 54−55 °C; ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3 H), 4.67 (s, 2 H), 5.12 (br s, 2 H), 6.97 (d, 1 H, $J = 8.9$ Hz), 7.46 (dd, 1 H, $J = 2.8, 8.9$ Hz), 8.13 (d, 1 H, $J = 2.8$ Hz), 10.9 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.3, 74.2, 114.5, 115.7, 119.3, 127.7, 133.3, 134.5, 138.3, 155.8, 164.3; IR ($CHCl_3$) 3300, 1740, 1600, 1483, 1452, 1415, 995, 912 cm^{-1}. Anal. Calcd for $C_{11}H_{11}ClO_3$: C, 58.29; H, 4.89; Cl, 15.64. Found: C, 58.59; H, 4.92; Cl, 15.90.

Kinetic Measurements for the Claisen Rearrangement of 9. Allyl ester **9** was heated as an oil to the desired temperature in a 500-mL, four-neck, round-bottom flask. Temperature control was maintained with an I^{2}R THERM-O-WATCH, equipped with a type K thermocouple and digital temperature readout. Aliquots of 40−60 mg were transferred into tared, 100-mL volumetric flasks, weighed, and diluted to the mark with 0.025 M aqueous NaH_2PO_4 (pH 3.0)/CH_3CN (40:60). The disappearance of **9** was monitored by HPLC analysis. Duplicate runs were performed at 175 °C, and the rate constants were ±10% from the average value. The measurements at 190 and 205 °C were not replicated. Plots of the natural logarithm of the area of the peak corresponding to **9** versus time and linear regressions were performed with the software Cricket Graph. Linear plots with correlation coefficients >0.990 were observed in all cases.

An analytically pure sample of 5-chloro-2-hydroxy-3-[(2-methyl-2-propenyl)oxy]benzoic acid 2-methyl-2-propenyl ester (**10**) was obtained by fractional vacuum distillation: bp 152 °C (7−8 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3 H), 1.83 (s, 3 H), 3.33 (s, 2 H), 4.67 (br s, 1 H), 4.75 (s, 2 H), 4.84 (br s, 1 H), 5.01 (br s, 1 H), 5.06 (br s, 1 H), 7.27 (d, 1 H, $J = 2.7$ Hz), 7.71 (d, 1 H, $J = 2.7$ Hz), 10.98 (br s, 1

H); ^{13}C NMR ($CDCl_3$) δ 19.5, 22.3, 37.0, 68.8, 112.4, 112.8, 114.0, 123.4, 127.0, 130.4, 135.9, 139.0, 143.4, 158.6, 169.2; IR ($CHCl_3$) 3176, 1677, 1608, 1437, 900 cm^{-1}. Anal. Calcd for $C_{15}H_{17}ClO_3$: C, 64.17; H, 6.10; Cl, 12.63. Found: C, 64.45; H, 6.18; Cl, 12.83.

Kinetic Measurements for the Claisen Rearrangement of 11a. 5-Chloro-2-[(2-methyl-2-propenyl)oxy]benzoic acid (**11b**, 2.5 g, 0.011 mol) was weighed into a 250-mL volumetric flask and diluted to the mark with 0.045 M aqueous NaOH to afford a homogeneous solution of **11a**. This solution was transferred to a 450-mL stainless steel Parr reaction vessel, sealed, and heated to the desired temperature. After a 20-min equilibration at the desired temperature, reaction aliquots were taken at timed intervals (1 mL was diluted to the mark in a 25-mL volumetric flask with 0.025 M aqueous NaH_2PO_4 (pH 3.0)/CH_3CN (40:60)) and analyzed by HPLC. Duplicate runs were performed at 170 and 185 °C. The rate constants were ±5% from the average value. The measurement at 155 °C was not replicated. Plots of the natural logarithm of the area of the peak corresponding to **11b** versus time and linear regressions were performed with the software Cricket Graph. Linear plots with correlation coefficients >0.990 were observed in all cases.

An analytically pure sample of 5-chloro-2-hydroxy-3-[(2-methyl-2-propenyl)oxy]benzoic acid (**12b**) was obtained after reslurrying in toluene/hexanes: mp 119−120 °C; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3 H), 3.35 (s, 2 H), 4.68 (br s, 1 H), 4.86 (s, 1 H), 7.34 (d, 1 H, J = 2.7 Hz), 7.77 (d, 1 H, J = 2.7 Hz), 10.51 (br s, 1 H, phenol); ^{13}C NMR ($CDCl_3$) δ 22.3, 37.0, 111.6, 112.6, 123.9, 128.0, 130.8, 137.3, 143.2, 159.1, 174.3; IR ($CHCl_3$) 3080, 1665, 1609, 1435, 1295, 888 cm $^{-1}$. Anal. Calcd for $C_{11}H_{11}ClO_3$: C, 58.29; H, 4.89; Cl, 15.64. Found: C, 58.52; H, 4.99; Cl, 15.68.

General Procedure Employed in the Statistical Experimental Design Study of the Saponification of Allyl Ester 9, Claisen Rearrangement of 11a, and Ring Closure with HCl. A solution of ester **9** (20 g, 0.07 mol) in toluene (prepared as described above) was combined with a solution of NaOH and (n-Bu)$_4$NHSO$_4$ in deionized water in a four-neck, 500-mL, round-bottom flask equipped with a Dean−Stark trap. The quantities of NaOH, (n-Bu)$_4$NHSO$_4$, and water were varied relative to **9** based upon the stoichiometries shown in Table 2. This mixture was heated, and toluene was removed by azeotropic distillation. After removal of the toluene, the reaction was refluxed (~100 °C) until a homogeneous solution was obtained. The in situ yield of **11a** was determined by HPLC.

The resulting solution of the sodium carboxylate was diluted to 250 mL in a volumetric flask and transferred to a 450-mL stainless steel Parr reaction vessel. The stirred mixture was heated to 170 °C over approximately 50 min and held at that temperature for 6 h.

The product solution from the Claisen rearrangement was transferred to a four-neck, 500-mL, round-bottom flask and acidified with concd HCl (73 mL). The slurry was heated to reflux (100−105 °C) and stirred at reflux for 6 h. The mixture was cooled to 80−90 °C, and toluene (100 mL) was added. The layers were separated, and the aqueous layer was reextracted with toluene (100 mL). The toluene extracts were combined in a four-neck, 500-mL, round-bottom flask equipped with a Dean−Stark trap. The solution was heated, and toluene was distilled to a final reaction volume of approximately 75 mL. The solution was allowed to cool to ambient temperature, then cooled in an ice bath, and stirred for 2 h. The slurry was filtered, and the filter cake was washed with chilled toluene (25 mL). The product was dried under vacuum at 35 °C to afford **6**, which was analyzed by HPLC for potency versus an analytically pure reference standard.

5-Chloro-2-hydroxy-3-(2-methyl-1-propenyl)benzoic Acid (13b). A solution of **9** (25 g, 0.089 mol) in toluene (61.3 mL of solution) was combined with an aqueous solution of (n-Bu)$_4$NHSO$_4$ (0.76 g, 2.2 mmol) and NaOH (7.3 g, 0.18 mol) in water (250 mL) and refluxed while toluene was removed azeotropically. The reaction was refluxed until a homogeneous solution was obtained (~5 h). The solution (pH 13.0) was diluted to 250 mL and transferred to a 450-mL stainless steel Parr reactor. The reaction mixture was heated to 170 °C and held for 33.25 h. After being cooled to ambient temperature, the reaction mixture was transferred to a 500-mL, round-bottom flask. An oil layer was present. The mixture was extracted with toluene (2 × 100 mL). The aqueous phase was adjusted to pH 1.8 with concd HCl to afford a beige slurry. After being stirred for 2 h at 0 °C, the slurry was filtered and washed with water (100 mL). The product was recrystallized from toluene/hexanes to afford 8.0 g (40%) of **13b** as an off-white solid, which contained approximately 5% of **12b** as determined by ^{1}H NMR analysis. Compound **13b**: ^{1}H NMR ($CDCl_3$) δ 1.80 (br s, 3 H), 1.94 (br s, 3 H), 6.24 (br s, 1 H), 7.36 (d, 1 H, J = 2.7 Hz), 7.75 (d, 1 H, J = 2.7 Hz), 10.7 (br s, 1 H, phenol); ^{13}C NMR ($CDCl_3$) δ 19.6, 26.6, 111.5, 118.0, 123.6, 127.6, 129.8, 137.0, 138.7, 158.6, 174.1; IR ($CHCl_3$) 3089, 1667, 1604, 1426, 1191, 886 cm^{-1}. Anal. Calcd for $C_{11}H_{11}ClO_3$: C, 58.29; H, 4.89; Cl, 15.64. Found: C, 58.05; H, 4.86; Cl, 15.85.

Identification of Claisen Rearrangement Byproducts. Following an aqueous Claisen rearrangement as described above, a reaction solution was extracted with toluene (100 mL). The toluene solution was extracted with 1 N NaOH (2 × 50 mL) and then concentrated to leave 3.7 g of a dark oil. Flash chromatography on silica gel with 1:11.5 EtOAc/hexanes as eluent gave 0.14 g of 5-chloro-2,3-dihydro-2,2-dimethylbenzofuran (**16**) and 0.70 g of a mixture of the olefins 4-chloro-2-(2-methyl-2-propenyl)phenol (**14b**) and 4-chloro-2-(2-methyl-1-propenyl)phenol (**15b**).

The mixture of **14b** and **15b** was examined. Major component (**15b**): ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.92 (s, 3 H), 5.18 (s, 1 H, phenol), 6.04 (s, 1 H), 6.80 (d, 1 H, J = 8.6 Hz), 7.02 (d, 1 H, J = 2.4 Hz), 7.08 (dd, 1 H, J = 2.4, 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 19.43, 22.01, 116.09, 117.62, 124.73, 126.16, 127.92, 129.40,141.72, 151.45; GC−MS (EI) m/z 184 (M + 2, 32), 182 (M, 100), 167 (96), 77 (71). Minor component (**14b**): ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3 H), 3.31 (s, 2 H), 4.83 (s, 1 H), 4.92 (s, 1 H), 5.37 (s, 1 H, phenol), 6.74 (d, 1 H, J = 9.4 Hz), 7.06−7.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 39.5, 112.9, 117.6, 125.3, 126.6, 127.7, 130.4, 143.8, 153.3; GC−MS (EI) m/z 184 (M + 2, 28), 182 (M, 90), 167 (84), 77 (100). Anal. Calcd for

$C_{10}H_{11}ClO$:[42] C, 65.76; H, 6.07; Cl, 19.41. Found: C, 66.20; H, 6.21; Cl, 19.23.

Benzofuran **16**: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 6 H), 2.96 (s, 2 H), 6.61 (d, 1 H, $J = 8.4$ Hz), 7.03 (d, 1 H, $J = 8.4$ Hz), 7.06 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.0, 42.7, 87.4, 110.3, 124.4, 125.2, 127.7, 129.0, 157.5; GC−MS (EI) *m/z* 184 (M + 2, 26), 182 (M, 83), 167 (100), 77 (58).

Claisen Rearrangement of 11a and Ring Closure with Amberlyst 15. Carboxylic acid **11b** (3.7 g, 0.016 mol) was combined with 1 N NaOH (18 mL) in a 25-mL volumetric flask and diluted to 25 mL with deionized water. The solution was transferred to a 50-mL Parr reactor with 10 mL of deionized water, heated to 170 °C, and held for 5.5 h. The reactor contents were allowed to cool to 25 °C, transferred to a 125-mL Erlenmyer flask, and adjusted to pH 2.0 with 6 N HCl (3 mL). The slurry was extracted with DCE (2 × 25 mL). The combined organic phase was diluted with DCE (25 mL) and washed with brine (35 mL). The organic solution of **12b** was transferred to a 250-mL, three-neck, round-bottom flask. The aqueous phase was back-extracted with DCE (25 mL), and the extract was combined with the product solution. Solvent (20 mL) was distilled off, and Amberlyst 15 (0.75 g) and DCE (20 mL) were added. The stirred mixture was held at reflux for 5 h and then filtered. The resin was washed with DCE (20 mL). The filtrate was combined with toluene (35 mL) and distilled until a pot temperature of 110 °C was achieved. The concentrate was allowed to cool to ambient temperature. Toluene (5 mL) was added. The slurry was cooled in an ice bath and filtered. The filter cake was washed with chilled toluene and dried under vacuum at 35 °C to afford 2.8 g (75%) of **6**, which was ≥99% pure by HPLC analysis.

Tropinone (7) from Dimethoxytetrahydrofuran. An aqueous solution (50 mL) of 2,5-dimethoxytetrahydrofuran (**17**) (20.4 g, 0.154 mol) was charged with concd HCl (2 mL, 0.025 mol) and was heated at 70−75 °C for 30 min. The mixture was cooled to ambient temperature. To a 500-mL, four-neck flask fitted with a thermometer, pH probe, mechanical stirrer, and N_2 inlet were charged water (150 mL), NaOAc (50.0 g, 0.61 mol), $MeNH_2$ (15 mL, 40% aqueous solution, 0.17 mol), concd HCl (14.2 mL, 0.18 mol), and acetonedicarboxylic acid (24.8 g, 0.17 mol). The solution (pH 5.1) was cooled to 10 °C, and the dialdehyde solution was charged over 10 min (final pH at end of addition was 5.1). The mixture was warmed to 40 °C over 10 min, stirred at 40 °C for 50 min, and then cooled to 20 °C. Sodium hydroxide (12.5 mL of 50% solution) was added to bring the solution to pH 10. After addition of NaCl (40 g) and complete dissolution, the aqueous solution was extracted with CH_2Cl_2 (3 × 85 mL). The combined CH_2Cl_2 layers were concentrated to give 18.7 g of an off-white solid (90% yield), **7**: mp 40−42 °C (lit.[43] mp 42−44 °C). The spectral data were identical to those of an authenic sample (Aldrich Chemical Company Inc.) with respect to the ^{1}H and ^{13}C NMR.

Tropinone (7) from Butanedial. A 2-L, four-neck, round-bottom flask was charged with water (650 mL) and NaOAc (214 g, 2.6 mol). After all of the acetate had dissolved, $MeNH_2$ (55 mL, 40% aqueous solution, 0.64 mol) was added. After cooling to below 10 °C, concd HCl (56 mL, 0.69 mol) was added at such a rate that the temperature was maintained below 10 °C. Acetonedicarboxylic acid (106 g, 0.73 mol) was added, and the solution was stirred until homogeneous.[44] Butanedial (110 mL, 40% aqueous solution, 0.580 mol) was then added to the cooled solution over 10 min, while the temperature was maintained at 10−15 °C. The reaction mixture was warmed to 40 °C at such a rate as to control CO_2 evolution and was then stirred at 40 °C until effervescence stopped. The mixture was then cooled to below 15 °C and adjusted to pH 10 with 50% aqueous NaOH. Sodium chloride (100 g) was added, and the solution was extracted with CH_2Cl_2 (4 × 125 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to provide 67 g of **7** (94% yield, 99% potency by GC assay).[45]

General Procedure Employed in the Statistical Experimental Design Study of the Reductive Amination of 7 with $NaBH(OAc)_3$. In a 100-mL, three-neck flask equipped with a mechanical stirrer and a N_2 purge were placed tropinone (**7**) (1.40 g, 0.010 mol) and CH_2Cl_2 (40 mL). Acetic acid, benzylamine, and $NaBH(OAc)_3$ were added, and the reaction mixture was stirred at ambient temperature for 22 h.[46] The quantities of acetic acid, benzylamine, and $NaBH(OAc)_3$ were varied relative to tropinone based upon the stoichiometries shown in Table 4. The reaction was quenched by the slow addition of 5 M NaOH (40 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum to provide benzyltropanamine (**21**). The endo:exo product ratio and the percent of *N*-benzylacetamide were measured by GC analysis of a representative reaction mixture sample.

3-*endo*-Tropanamine (8) from $NaBH(OAc)_3$. In a 500-mL, three-neck flask equipped with a mechanical stirrer, a reflux condenser, and a N_2 purge were placed $NaBH_4$ (2.84 g, 0.075 mol) and CH_2Cl_2 (150 mL). Acetic acid (15.75 g, 0.26 mol) was added to the suspension by a syringe pump over 3−4 h, and the reaction mixture was stirred at ambient temperature under a N_2 atmosphere until the hydrogen evolution was complete (5 h). Tropinone (6.95 g, 0.050 mol) and benzylamine (7.2 g, 0.068 mmol) in CH_2Cl_2 (50 mL) were added, and the reaction mixture was stirred at ambient temperature until reaction was complete by GC analysis (15−22 h). The reaction was quenched by the slow addition of 5 M NaOH (200 mL). The organic layer was separated, washed with 5 M NaOH (200 mL), and extracted with 2 M HCl (80 mL). The aqueous layer was separated and adjusted to pH 9 with 50% NaOH. The aqueous benzyltropanamine solution was transferred into a Parr shaker bottle, and 5% Pd/C catalyst (2.3 g) was added to the solution. The solution was hydrogenated at 70 °C and 50 psig until the reaction was complete as indicated by GC analysis (4−10 h). The

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(42) Analysis was performed on a mixture of isomers (**14b** and **15b**).

(43) *Beilstein 21,* 258.

(44) If the solution is warmed prior to addition of the butanedial, decarboxylation of the diacid begins to occur, resulting in lower yields.

(45) In the course of our development work, several impurities were identified and analyzed by GC−mass spectrometric analysis. These impurities included *N*-methylpyrrole, the *N*-methyl imine of tropinone, the tertiary alcohol derived from acetone addition to the carbonyl of tropinone, and 3-(methylamino)cyclohept-6-enone.

(46) Sodium triacetoxyborohydride (95%) for this study was purchased from Aldrich Chemical Company and used without further purification.

catalyst was filtered through Hyflo Super Cel, and the resulting aqueous solution was used directly in the Schotten−Baumann acylation.

3-*endo*-Tropanamine Dihydrochloride from Tris[(2-ethylhexanoyl)oxy]borohydride. In a 500-mL, three-neck flask equipped with a mechanical stirrer, a reflux condenser and a N_2 purge were placed $NaBH_4$ (3.78 g, 0.10 mol) and CH_2Cl_2 (150 mL). 2-Ethylhexanoic acid (50.5 g, 0.350 mol) was added to the suspension by a syringe pump over 4−5 h, and the reaction mixture was stirred at ambient temperature under a N_2 atmosphere until the hydrogen evolution was complete (15 h). Tropinone (6.25 g, 0.045 mol) and benzylamine (8.0 g, 0.075 mol) in CH_2Cl_2 (50 mL) were added, and the reaction mixture was stirred at ambient temperature until reaction was complete by GC analysis (15−22 h). The reaction was quenched by the slow addition of 5 M NaOH (200 mL). The organic layer was separated, washed with 5 M NaOH (200 mL), and extracted with 2 M HCl (80 mL). The aqueous layer was separated and adjusted to pH 9 with 50% NaOH solution. The aqueous benzyltropanamine solution was transferred into a Parr shaker bottle, and 5% Pd/C catalyst (2.3 g) was added to the solution. The solution was hydrogenated at 70 °C and 50 psig until the reaction was complete as indicated by GC analysis (4−10 h). The catalyst was filtered through Hyflo Super Cel, and the filtrate was adjusted to pH 12 with 50% NaOH. The aqueous layer was extracted with CH_2Cl_2 (200 mL). The dihydrochloride salt was precipitated from the CH_2Cl_2 layer by slow bubbling of HCl gas through the solution. The product was filtered and dryed in vacuo to afford 8.15 g of 3-*endo*-tropanamine dihydrochloride salt (85%) as a white solid: mp >250 °C dec; ^{1}H NMR (D_2O)[47] δ 2.17 (d, J = 9.8 Hz, 2 H), 2.25 (d, J = 17.3 Hz, 2 H), 2.53 (m, 2H), 2.60 (ddd, J = 17.3, 7.5, 7.2 Hz, 2H), 2.82 (s, 3H), 3.78 (t, J = 7.5 Hz, 1H), 4.01 (br s, 2H); ^{13}C NMR (D_2O) δ 25.9, 35.3, 41.5, 43.0, 64.1; IR (KBr) 3010, 2919, 2874, 1612, 1585, 1521 cm^{-1}. Anal. Calcd for $C_8H_{16}N_2 \cdot 2HCl$: C, 45.08; H, 8.51; N, 13.14. Found: C, 45.08; H, 8.64; N, 13.23.

5-Chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carbonyl Chloride (24). A toluene solution (30 mL) of benzofurancarboxylic acid (**6**) (10 g, 0.044 mol) was charged with a catalytic amount of DMF (0.1 mL) and was warmed to 45−50 °C. A toluene (7 mL) solution of $SOCl_2$ (6.31 g, 0.053 mol) was added dropwise to the carboxylic acid solution. Reaction progress was followed by GC assay (a 0.2-mL aliquot was diluted in 10 volumes of toluene). The acid chloride formation was complete in less than 2 h.

***endo*-5-Chloro-2,3-dihydro-2,2-dimethyl-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)benzofuran-7-carboxamide (25).** To a 250-mL, round-bottom flask fitted with a mechanical stirrer was charged water (55 mL), toluene (10 mL), 50% NaOH (4.24 g, 0.053 mol), and tropanamine (7.42 g, 0.053 mol, based on a quantitative yield from the tropanamine synthesis described above). The amine solution was cooled to below 10 °C in an ice water bath, and the acid chloride solution (prepared by the method described above) was added to the basic tropanamine solution at such a rate that the temperature stayed below 10 °C. The mixture was maintained above pH 7.5 by the dropwise addition of 5 M NaOH. After the addition of the acid chloride was complete, the mixture was warmed to 50 °C for 2 h. The reaction mixture was monitored by GC assay for the presence of acid chloride and the presence of residual tropanamine. When the reaction was complete, the phases were separated, and the organic layer was extracted with 1 N HCl (45 mL). The product was precipitated by adjusting the combined aqueous extracts to pH 11 by the addition of 50% NaOH (typically 1.9 equiv of NaOH). After stirring for 2 h below 5 °C, the product was filtered, washed with water (35 mL), and dried under vacuum (45 °C) to afford 13.5 g of **25** (88%) as a white solid: mp 200−205 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3H), 1.62 (d, 2H, J = 14.2 Hz), 1.87 (m, 2H), 2.10 (m, 2H), 2.21 (m, 2H), 2.25 (s, 3H), 3.0 (s, 2H), 3.11 (bs, 2H), 4.25 (dt, J = 7.1, 14.6 Hz, 1H), 7.13 (m, 1H), 7.81 (d, J = 2.1 Hz, 1H) 8.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 28.0, 36.4, 40.0, 40.3, 41.7, 59.9, 90.1, 116.9, 125.6, 128.0, 128.4, 129.7, 154.6, 161.9; IR (KBr) 3399, 2932, 1660, 1540, 1444, 1284, 1136 cm^{-1}.

***endo*-5-Chloro-2,3-dihydro-2,2-dimethyl-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)benzofuran-7-carboxamide Maleate (1).** A 250-mL, three-neck, round-bottom flask, equipped with a mechanical stirrer, thermometer, and condenser, was charged with zatosetron free base (**25**) (9.0 g, 0.026 mol) and EtOH (20 mL). The stirred slurry was heated to 45−50 °C, and a solution of maleic acid (3.7 g, 0.032 mol) in EtOH (20 mL) was added. The reaction mixture, which became homogeneous upon addition of the maleic acid, was heated to 75−80 °C, and the resulting hot solution was filtered to remove insoluble materials. Hot EtOAc (45 mL, 70 °C), was added to the filtrate while refluxing was maintained. The refluxing solution was seeded and cooled slowly to 0−5 °C over 4 h. After the mixture was stirred at 0−5 °C for 2 h, the product was removed by filtration, washed with cold EtOAc (25 mL), and dried under vacuum (50 °C) to give 9.9 g (80%) of **1** as a crystalline white solid: mp 184−186 °C (lit.[2] mp 184−186 °C).

Acknowledgment

The authors gratefully acknowledge Mr. Ross A. Johnson for NMR analyses and Mr. Gary Thomas and Mr. Stephen Gregg for mass spectral analyses. Additionally, we are greatly indebted to Dr. Bruce Cooper, Dr. Paul Tsang, and Ms. Nancy Lockwood for developing the GC and HPLC assays to determine isomeric ratios of products.

Received for review March 4, 1997.[⊗]

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(47) ^{1}H and ^{13}C NMR spectra show the presence of a minor conformational isomer due to the configuration of the protonated tertiary amine (equitorial vs axial proton). Coalescence of the conformers occurs upon the addition of NaOD to the NMR sample.

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.