Organic Process Research & Development **2001**, *5*, 479–490

Development of an Efficient and Stereoselective Manufacturing Route to Idoxifene

Karl W. Ace, Mark A. Armitage, Richard K. Bellingham,* Paul D. Blackler, David S. Ennis,† Nigel Hussain, David C. Lathbury,† David O. Morgan, Noah O'Connor, Graham H. Oakes,‡ Stephen C. Passey,§ and Laurence C. Powling

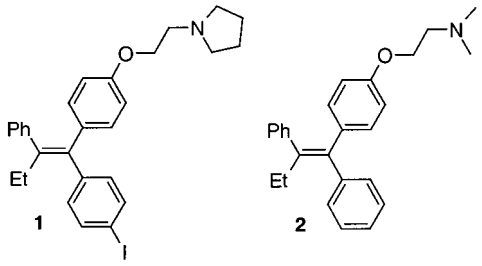
Chemical Development, GlaxoSmithKline Pharmaceuticals, Old Powder Mills, Nr. Leigh, Tonbridge, Kent TN11 9AN, U.K.

Abstract:

A literature route to 1-(2-{4-[(*E*)-1-(4-iodophenyl)-2-phenyl-but-1-enyl]phenoxy}ethyl)pyrrolidine (idoxifene) has been modified to tackle various scale-up issues and provide initial supplies. A new highly efficient, robust, and stereoselective manufacturing route is described in detail. This route involves diastereoselective synthesis of tertiary alcohol (1*RS*,2*SR*)-1-(4-iodophenyl)-2-phenyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)phenyl]butan-1-ol by Grignard addition to the ketone 1-(4-iodophenyl)-2-phenyl-1-butanone followed by derivatisation and stereoselective syn elimination to provide idoxifene in excellent yield and geometric purity. Evaluation of a more direct route to idoxifene using a McMurry low-valent titanium coupling reaction is also described.

Introduction

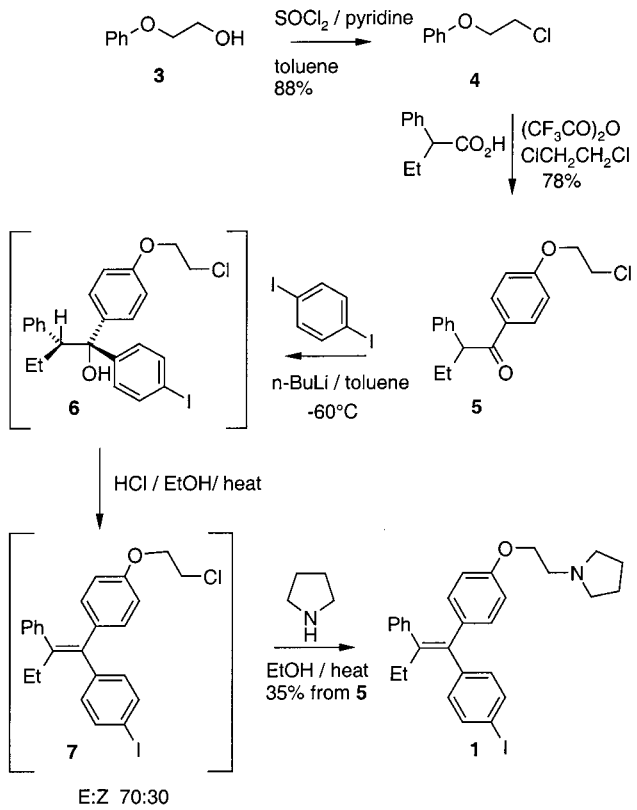
Idoxifene **1**, was first synthesised in 1986 by the Cancer Research Campaign[1] (CRC) and was licensed from the British Technology Group. Idoxifene **1** is a selective estrogen receptor modulator (SERM). It has estrogen agonist effects in bone tissue and upon lipid metabolism and estrogen antagonist effects in the uterus and breast tissues.[2−7] This broad profile gave idoxifene **1** the potential to treat or prevent several diseases associated with female menopause. Osteoporosis prevention was the lead indication, but clinical trials were also being conducted with idoxifene **1** in the treatment of advanced breast cancer, currently treated with the closely related compound tamoxifen **2**. This paper will briefly discuss the initial supply route, which was subtley modified from that previously reported,[8] and will then describe the evaluation of a very direct route using McMurry chemistry[9] and the development of a new, efficient, and stereoselective route.



Results and Discussion

The route shown (Scheme 1) was used to produce material on an 18-kg scale. The route differs from that previously

Scheme 1. **Route of synthesis used to prepare initial supplies**



* To whom correspondence should be addressed. Chemical Development, GlaxoSmithKline Pharmaceuticals, Old Powder Mills, Nr. Leigh, Tonbridge, Kent TN11 9AN, U.K. E-mail: Richard_K_Bellingham@sbphrd.com.

† Present address: Process R&D, AstraZeneca Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5HT, U.K.

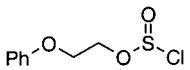
‡ Present address: University of Liverpool, Department of Chemistry, Crown Street, Liverpool L69 7ZD, U.K.

§ Present address: School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.

(1) McCague, R. Br. Patent GB 2174088, 1986.
(2) McCague, R.; Leclercq, G.; Legros, N.; Goodman, J.; Backburn, G. M.; Jarman, M.; Foster, A. B. *J. Med. Chem.* **1989**, *32*, 2527.
(3) Rowlands, M. G.; Parr, I. B.; McCague, R.; Jarman, M.; Goddard, J. M. *Biochem. Pharmacol.* **1990**, *40*, 283.
(4) Chander, S. K.; McCague, R.; Luqmani, Y.; Newton, C.; Dowsett, M.; Jarman, M.; Coombes, R. C. *Cancer Res.* **1991**, *51*, 5851.
(5) Haynes, B. P.; Parr, I. B.; Griggs, L. J.; Jarman, M. *Breast Cancer Res. Treat.* **1991**, *19*, 174.
(6) Hardcastle, I. R.; Rowlands, M. G.; Houghton, J.; Parr, I. R.; Potter, G. A.; Jarman, M. *J. Med. Chem.* **1995**, *38*, 241.
(7) Hardcastle, I. R.; Rowlands, M. G.; Grimshaw, R. M.; Houghton, J.; Jarman, M.; Sharff, A.; Neidle, S. *J. Med. Chem.* **1996**, *39*, 999.

10.1021/op0100394 CCC: $20.00
Published on Web 08/22/2001

published[8] in a number of key areas. The original route involved isolation of the intermediate chlorosulphite **8**, formed by reaction of alcohol **3** with excess thionyl chloride, and subsequent reaction with catalytic pyridine to give the chloroalkane **4**.

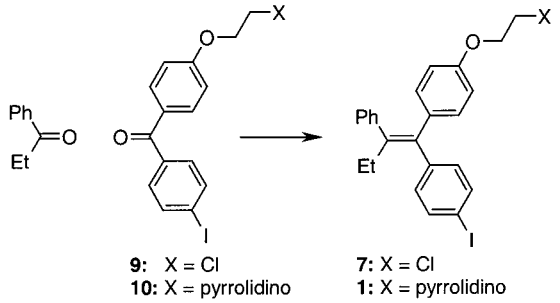


8

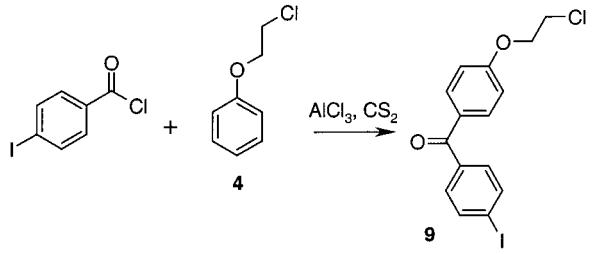
The uncontrolled evolution of sulphur dioxide was a major concern and led to the development of a method that premixed the alcohol **3** and 1 mol equiv of pyridine at reflux in toluene before the addition of 1 mol equiv of thionyl chloride. In this way the evolution of sulphur dioxide could be controlled by addition rate. Formation of ketone **5** from 2-phenylbutyric acid was initially performed neat, but on scale-up, addition of a solvent, primarily as a heat sink, was necessary. Isolation of the ketone **5** was modified by dilution of the reaction mixture with toluene before aqueous work-up. Crystallisation of the product **5** was then achieved by concentration followed by dilution with petroleum ether (80−100). Another key issue was the instability of 4-iodophenyllithium over time. On large scale the rate at which ketone **5** could be safely added severely limited batch size. The problem was overcome by adding butyllithium to a mixture of 1,4-diiodobenzene and ketone **5**; this approach was the subject of a previous publication.[10] Changing the solvent from THF to toluene also lowered levels of a dimeric impurity formed in this reaction.[10] Alcohol **6** and alkene **7** were not isolated but taken forward to crude idoxifene **1**. Separation of the geometric isomers was achieved by crystallisation to afford pure idoxifene **1**. Despite these improvements in the supply route there still remained some major drawbacks of this procedure. The low-temperature lithiation, which also leads to the formation of one mole equivalent of butyl iodide, and a lack of selectivity with respect to alkene **7** geometry meant that in the long term a new route was required.

McMurry Approach. As part of the program directed at identifying alternative routes to idoxifene **1**, it was considered that a low-valent titanium-meditated coupling (McMurry reaction[9]) between propiophenone and diaryl ketone **9** (Scheme 2) may provide a very direct route to the final product. It has been reported that the reaction works particularly well if one of the components is a diaryl ketone.[11] The related antitumour agent tamoxifen **2** has been successfully prepared by this approach.[12,13]

Scheme 2



Scheme 3



Propiophenone is commercially available, and the benzophenone **9** was prepared in one step via a Friedel−Crafts acylation reaction in 62% yield (Scheme 3).

Using the $TiCl_3$−Li protocol[11,12] the coupling was performed in DME to afford a 25% yield of the desired *E*-olefin **7** (Table 1, entry 1). A number of other systems were investigated (Table 1, entries 2−4) although none offered any significant advantage in terms of stereoselectivity or yield. In most cases the *E*-isomer **7** was the predominant product. Changing the solvent to THF had a pronounced effect on the stereoselectivity of the coupling. In both cases (Table 1, entries 5 and 6) the *Z*-olefin was observed as the predominant product. The effect of the solvent in controlling the stereochemistry of the McMurry reaction has been reported previously.[14]

Since the choice of solvent appeared to be important in controlling stereoselectivity, a number were evaluated. No reaction was observed in acetonitrile, DME, dioxolane, or thioxane (Table 1, entries 7−10); however in 1,4-dioxane a considerable predominance of the desired *E*-olefin **7** was observed (Table 1, entry 11). These results suggested that dioxygenated solvents form stable octahedral titanium complexes.[15] It was reasoned that bidentate ligands capable of complexing the titanium in a similar manner could also influence the stereoselectivity of the reaction. A number of reactions were performed in 1,4-dioxane in the presence of various bidentate phosphine and amine ligands (Table 1, entries 13−16). Although the *E*-isomer **7** was the predominant product in all cases, only the reaction containing 1,2-bis(diphenylphosphino)ethane (Table 1, entry 13) offered any advantage in terms of stereoselectivity and yield.

(8) McCague, R.; Potter, G. A.; Jarman, M. *Org. Prep. Proced. Int.* **1994**, *26*(3), 343.
(9) (a) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041. (b) McMurry, J. E.; Fleming, M. P.; *J. Am. Chem. Soc.* **1974**, *96*, 4708. (c) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255. (d) Robertson, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford; 1991, p 563.
(10) Ennis, D. S.; Lathbury, D. C.; Wanders, A.; Watts, D. *Org. Process Res. Dev.* **1998**, *2(5)*, 287.
(11) (a) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.
(12) Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475.
(13) (a) Shani, J.; Gazit, A.; Livshitz, T.; Biran, S. *J. Med. Chem.* **1985**, *28*, 1504. (b) Schwartz, W.; Hartmann, R. W.; Schonenberger, H. *Arch. Pharmacol.* **1991**, *324*, 223. (c) Gauthier, S.; Mailhot, J.; Labrie, F. *J. Org. Chem.* **1996**, *61*, 3890.
(14) Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1991**, *56*, 1940.
(15) Reetz, M. T. In *Organotitanium Reagents in Organic Synthesis*; Springer Verlag: Berlin, 1986; p 21.

Table 1.

entry	conditions	additive	solvent	*E*:*Z* ratio	*E* (%) isolated	*Z* (%) isolated
1	$TiCl_3$−Li	none	DME	1.8:1	26	14
2	$TiCl_4$−Zn	none	DME	1.3:1	20	15
3	$TiCl_3$-LAH	none	DME	1.4:1	30	21
4	$TiCl_3(dme)_{1.5}$−Zn−Cu	none	DME	1:1	6	6
5	$TiCl_4$−Zn	none	THF	1:1.9	-	-
6	$TiCl_3$-LAH	none	THF	1:11	-	-
7	$TiCl_4$−Zn	none	MeCN	no reaction	-	-
8	$TiCl_4$−Zn	none	glyme	no reaction	-	-
9	$TiCl_4$−Zn	none	1,3-dioxolane	no reaction	–	–
10	$TiCl_4$−Zn	none	1,4-thioxane	no reaction	–	–
11	$TiCl_4$−Zn	none	1,4-dioxane	3.9:1	45	11.5
12	$TiCl_4$−Zn	none	diethoxy methane	1.4:1	–	–
13	$TiCl_4$−Zn	dppe	1,4-dioxane	4.1:1	51	12
14	$TiCl_4$−Zn	dppp	1,4-dioxane	3.6:1	40	11
15	$TiCl_4$−Zn	PPh_3	1,4-dioxane	3.5:1	26	7.5
16	$TiCl_4$−Zn	TMEDA	1,4-dioxane	3.4:1	–	–

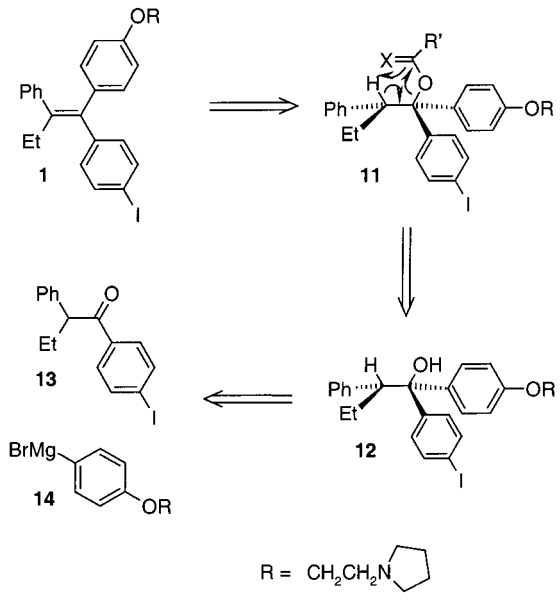
To demonstrate the utility of the McMurry reaction for the preparation of idoxifene **1,** the reaction was performed on a 25 mmol scale using the optimum conditions (Table 1, entry 13). After work-up the crude mixture of *E*- and *Z*-alkenes was reacted with pyrrolidine in refluxing ethanol to give a mixture of *E*- and *Z*-idoxifene. Purification by chromatography followed by recrystallisation from ethanol afforded *E*-idoxifene **1** in 21% yield from **9**. Idoxifene **1** could also be prepared directly from **10**, but this procedure was inferior in both stereoselectivity and yield. Although an extremely direct approach to idoxifene **1**, the route suffered from a lack of *E*:*Z* selectivity, and the inevitable chromatographic purification of the final product. Work in this area was discontinued.

Syn-Elimination Approach. During development work on the original synthetic route the intermediate tertiary alcohol **6** had been isolated.[10] Single-crystal X-ray diffraction experiments had demonstrated that tertiary alcohol **6** was obtained effectively as the single diastereoisomer[10] predicted by Cram's rule.[16] Much of this stereochemical information was lost in the acid-catalyzed dehydration reaction. It was therefore envisaged that much better *E*:*Z* ratios of idoxifene **1** could be obtained if a concerted elimination of a diastereomerically enriched substrate **11** could be performed (Scheme 4). The research pursued a syn-elimination approach; hence, synthesis of the tertiary alcohol **12** became the focus of our work.

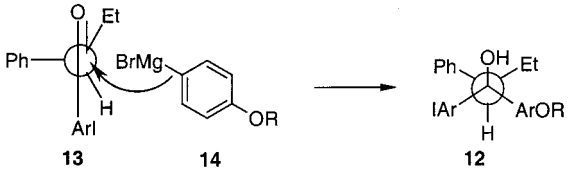
Alcohol **12** should be accessible by a Grignard addition of **14** to ketone **13** with the addition occurring via a Felkin−Anh transition state[17] (Scheme 5).

Synthesis of Ketone 13. Attempts to make the precursor ketone **13** initially centred around nucleophilic addition of 4-iodophenyllithium to various 2-phenylbutyric acid derivatives. The reaction of the Weinreb amide[18] **15** was the only procedure to give a synthetically useful yield of ketone **13** (48%) that was isolable without chromatography (Scheme 6). This procedure was used to prepare supplies of ketone **13** for laboratory-scale investigations on downstream chemistry.

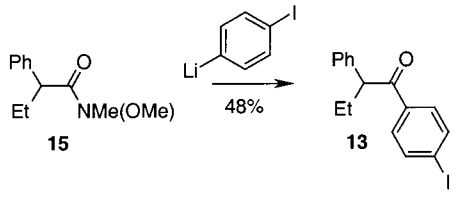
Scheme 4



Scheme 5

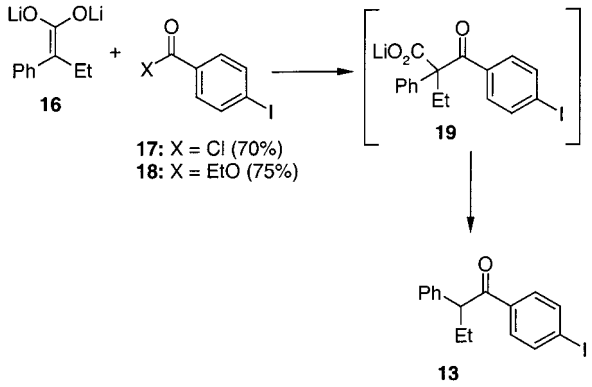


Scheme 6



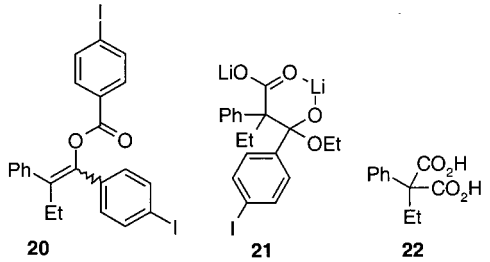
(16) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc*. **1952**, *74*, 5828.
(17) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, *9*, 2199. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(18) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20(8)*, 1105.

Scheme 7



To reduce iodinated waste and cost, approaches via 4-iodobenzoic acid derivatives were evaluated. Direct approaches via reaction of various benzylic anions with 4-iodobenzoic acid derivatives were unsuccessful. Formation of the dianion of phenylbutyric acid **16** and subsequent reaction with 4-iodobenzoyl chloride **17** gave a 70% yield of the desired ketone **13** on aqueous work-up (Scheme 7) without the need for a separate decarboxylation reaction. This result quickly led to the evaluation of ethyl-4-iodobenzoate **18** as a potential electrophile (Scheme 7). This reaction gave the desired ketone **13** in a comparable yield of 75%. Further work concentrated on optimisation of the reaction utilising ethyl-4-iodobenzoate **18** since this was by far the cheapest reagent. Formation of the dianion **16** was always performed by addition of 2-phenylbutyric acid solution to the LDA solution to prevent precipitation of the less soluble lithium carboxylate.

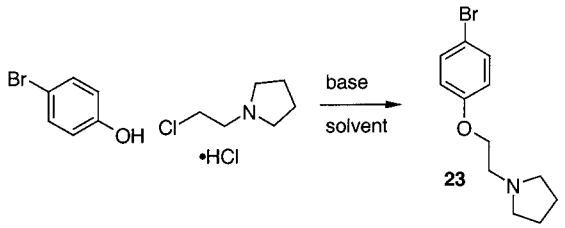
Before the reaction could be scaled up, a more detailed appreciation of the mechanism was needed, most importantly, the point in the reaction sequence at which the intermediate **19** underwent decarboxylation. The conditions established for synthesis of laboratory samples were the reaction of 2-phenylbutyric acid with LDA at room temperature, followed by addition of ester **18** in THF at 0 °C. The reaction was then quenched with 5 M hydrochloric acid and extracted into toluene. The toluene solution was then concentrated to a low volume and diluted with ethanol; this procedure was repeated until crystallisation of ketone **13** occurred. Initial work with 4-iodobenzoyl chloride **17** indicated that decarboxylation occurred before work-up since small quantities of the by-product enol ester **20** were isolated, suggesting that the enolate was present during the addition of 4-iodobenzoyl chloride. However, in the case of the ester **18** reaction, safety testing of the procedure showed that carbon dioxide evolution occurred with acidic work-up. These results led to the postulation that the intermediate **21** was involved and that the ethoxide group leaves on exposure to strong acid. Efforts to trap an intermediate of type **21** with bis electrophiles (diiodomethane and dimethyldichlorosilane) failed. On scale-up of the reaction with ester **18** the longer addition times of ester **18** to the dianion **16** led to the isolation of a new impurity[19] **22** that clearly indicated that decarboxylation occurred prior to acidic work-up since carbon dioxide had been trapped by the dianion **16**.



Online studies using the React-IR system eventually demonstrated that decarboxylation started at −25 °C and accelerated above −10 °C. The carbon dioxide was presumably being trapped in solution as an adduct with diisopropylamine. The results from the React-IR studies also showed that formation of dianion **16** and the reaction with ester **18** at room temperature took no longer than 30 min. These results led to the development of an inverse addition protocol where the dianion **16** solution could be added to a solution of ester **18** at room temperature. When the reaction was deemed complete, the solution was added to 5 M hydrochloric acid, carbon dioxide evolution being controlled by addition rate. The product isolation using solvent-exchange protocol was also replaced by a procedure that concentrated the toluene extract to two volumes and then diluted it with 2-propanol to precipitate the ketone **13**. This process has been used to synthesise ketone **13** reproducibly on >50 kg scale with yields of 77−94% and HPLC assay of >98.9%.

Synthesis of Aryl Bromide 23 and Grignard Reagent 14. Initial laboratory supplies of the bromide **23** were made via the Williamson ether synthesis from commercially available 4-bromophenol, *N*-(2-chloroethyl)pyrrolidine hydrochloride and sodium ethoxide in ethanol.[20] The bromide **23** can be purified by distillation and obtained pure on 100-g scale. The first batches produced on pilot-plant scale used a modification of this procedure using potassium carbonate as a base and 4-methyl-2-pentanone (MIBK) as a solvent (Scheme 8).

Scheme 8

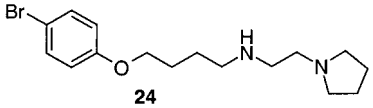


Base	Solvent	Temperature/°C	Yield
NaOEt	ethanol	78	74%
K_2CO_3	MIBK	118	65%

The quality of bromide **23** had a direct impact on the quality of idoxifene **1** produced. One of the major impurities

(19) Fadel, A.; Garcia-Argote, S. *Tetrahedron: Asymmetry* **1996**, *7(4)*, 1159.
(20) Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1982**, *47*, 2387.

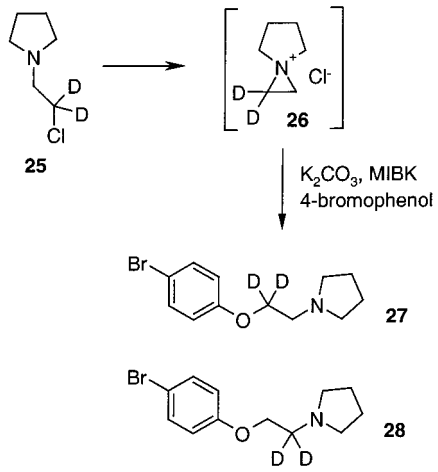
seen was the diamine **24** which was easily removed by employing a dilute aqueous zinc chloride wash to the procedure.



24

This method was used to synthesise bromide **23** on 30−35 kg scale in 65% yield. The mechanism of bromide **23** formation from chloroethyl pyrrolidine was briefly investigated, and the intermediacy of the aziridinium ion **26** was established (Scheme 9). The deuterated adduct **25** was made

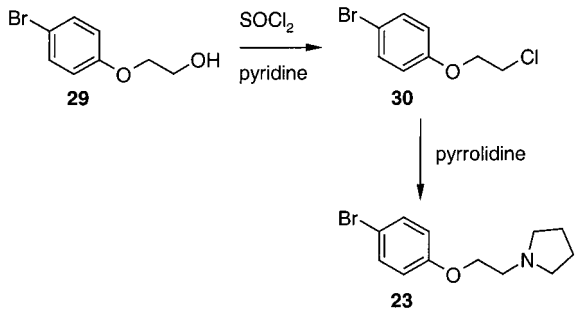
Scheme 9



by using standard literature methods.[21−23] The deuterated adduct **25** was reacted under standard conditions to give a 1:1 ratio of the products **27** and **28**.

Laboratory investigations into alternative routes to bromide[8] **23** led to a route that gave product **23** of extremely high purity (99.89% PAR HPLC) and in an overall yield of 63% (Scheme 10). However, supply of the aryl bromide **23**

Scheme 10



was out-sourced before the chemistry in Scheme 10 was scaled up.

Formation of the Grignard reagent **14** from bromide **23** was originally achieved on laboratory scale by reaction of ca. 10% of bromide **23** with activated magnesium[24] (1,2-dibromoethane) in THF. After the reaction had initiated, the remainder of the bromide was added at reflux. To obtain complete consumption of the bromide **23** 2.3 equiv of magnesium and 1 equiv of 1,2-dibromoethane had to be employed, and initiation at reflux was necessary. Further research showed that 1,2-dibromoethane was not needed if the THF was anhydrous, with initiation occurring at 62 °C. Evidence that initiation had occurred was essential for safe addition of the remainder of the aryl bromide **23**. An exothermic event close to the boiling point of a solvent is difficult to observe; therefore, the React-IR system was used in early laboratory studies to monitor the initiation. A characteristic band at 1036 cm^{-1} (tentatively assigned as a magnesium etherate stretch) was a clear indication that initiation had started. However, there were large differences in initiation times depending on the source of magnesium metal. To tackle this issue another method of activating magnesium[24] metal was employed. The addition of a small quantity (3.1 mol % with respect to (wrt) aryl bromide **23**) of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (65 wt % in toluene) solution provided more reproducible results and was used on several 20-kg batches, initiation occurring smoothly at 64 °C. Although the activation of magnesium metal with Red-Al had proved reliable, there were still a number of processing issues associated with its use:

(1) The viscous toluene solution was difficult to handle.

(2) Initiation occurred near the boiling point of THF causing the release of large quantities of vapour with the exothermic initiation.

(3) Only a limited amount of moisture in the THF was tolerated before the initiation failed.

(4) employment of Red-Al led to small quantities of hydrogen in the waste stream gases.

The release of large quantities of vapour on commencement of the reaction meant that very low vessel occupancy was essential such that initiation of the reaction did not cause a large increase in headspace pressure. To circumvent this problem it was desirable to have initiation of the reaction at low temperature such that the exotherm of reaction did not cause the solution to boil.

It was found that magnesium metal activated by the addition of 2.3 mol % (wrt aryl bromide **23**) of TMSCl reacted smoothly with the 10% charge of bromide **23** at 28 °C in GPR grade THF, causing an adiabatic temperature rise of 22 °C well below the boiling point of THF. The remainder of the bromide **23** is added below 50 °C followed by a 1 h reflux period. The TMSCl activation method of initiation tolerated up to 500 ppm water and up to 600 ppm of 2-hydroperoxy tetrahydrofuran in separate experiments. There was some dependence of the initiation time (5 to 40 min) on the source of THF, ironically a batch of anhydrous THF had the longest initiation time of 40 min, the exact reason for this variation was never deduced. Batches of THF that gave long initiation times gave short initiation times (ca. 5 min) after distillation. The only new impurity that arose

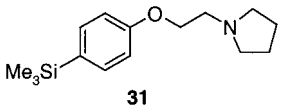
(21) Canonne, P.; Belley, M.; Fytas, G.; Plamondon, J. *Can. J. Chem.* **1988**; *66*, 168.

(22) Poindexter, G. S.; Owens, D. A.; Dolan, P. L.; Woo, E. *J. Org. Chem.* **1992**, *57*, 7(23), 6257.

(23) Cason J.; Baxter, W. M.; DeAcetis, W. *J. Org. Chem.* **1959**, *24*, 247.

(24) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996; pp 53−78.

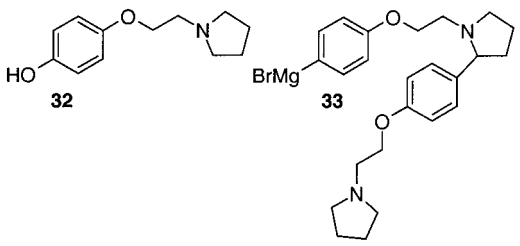
from the use of TMSCl to initiate the Grignard reaction was the aryl silane **31** and was never seen in the final product.



31

The TMSCl method to activate magnesium was successfully used with seven batches of bromide **23** on 20−45 kg scale. The concentration of the Grignard reagent **14** solution was established by titration of a sample against *s*-BuOH in *p*-xylene using 1,10-phenanthroline as indicator.[25] Towards the end of the project an on-line React-IR method had been successfully demonstrated in the pilot plant.

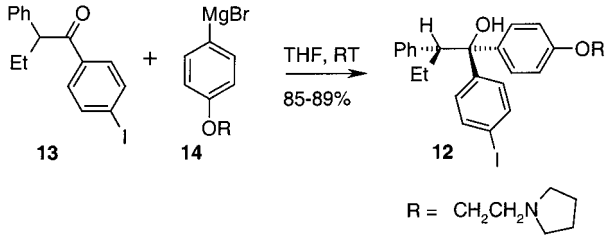
Throughout this research it was found that a rigorously anaerobic atmosphere (O_2 content <0.2%) was required; otherwise, two impurities (**32** and **33**) were observed at unacceptably high levels. The impurity **33** reacts with ketone **13** and is carried through to produce an idoxifene-related impurity that is not efficiently removed by recrystallisation.



32 **33**

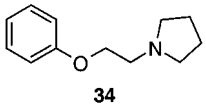
Synthesis of Tertiary Alcohol 12. Initially a 4-fold excess of Grignard reagent **14** was used to completely consume ketone **13** in THF with the alcohol **12** being obtained in a 79% yield essentially as a single diastereoisomer by ^{1}H NMR. Conditions were soon optimised to use 1.3 equiv of the Grignard reagent **14** and consistently obtain a yield of the alcohol **12** of 85−89% (Scheme 11). The relative

Scheme 11



stereochemistry was determined by single-crystal X-ray diffraction.

The phenyl ether **34** by-product formed on work-up was easily removed by slurrying the crude product in petroleum ether (60−80)/toluene (9:1).



34

Selection of Ester 11e and Optimisation of syn Elimination. In the early stages of the project the alcohol **12** was isolated as a white solid before being derivatised in the next

Scheme 12

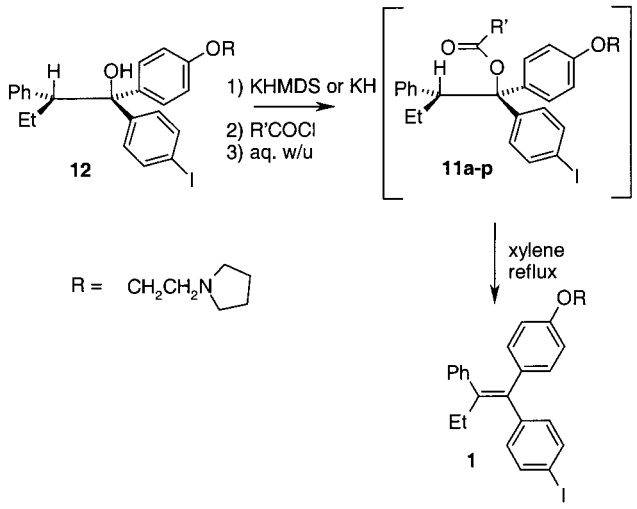


Table 2

	R′	reaction time/h	*E*:*Z* ratio at end of reaction	*E*:*Z* ratio after 1 h
11a	Me	4.5	79:21	85:15
11b	Et	3	71:29	77:23
11c	$MeOCH_2$	1	79:21	−
11d	Me_2CCH_2	2	88:12	89:11
11e	Me_3C	7.5	88:12	93:7
11f	MeO_2C	2	76:24	−
11g	$PhCH_2$	1	75:25	−
11h	Ph	1	77:28	−
11i	4-$(MeO)C_6H_4$	2	78:22	78:22
11j	4-$(NO_2)C_6H_4$	1	74:26	−
11k	2,4-$(MeO)_2C_6H_3$	8.5	88:12	94:6
11l	3,4,5-$(MeO)_3C_6H_2$	1	80:20	−
11m	2-$(MeO)C_6H_4$	2	89:11	90:10
11n	2-$(Me)C_6H_4$	2	81:19	84:16
11o	2-ClC_6H_4	1	79:21	−
11p	2-furyl	2	77:23	77:23

step. All derivatives of alcohol **12** were formed by reaction of electrophiles with the potassium alkoxide of **12** in THF at room temperature formed using either potassium hydride or potassium hexamethyldisilazide (KHMDS). A large number of functionalities (xanthate salts,[26] xanthate esters,[26] isocyanates, thioisocyanates, chlorosulphite, carbodiimide adducts, diphenyl phosphite, and acetate) were made and their high-temperature elimination reactions evaluated. Elimination of acetate **11a** yielded the highest *E*:*Z* ratios (79:21); hence, an extensive range of esters (again synthesised via the potassium alkoxide of alcohol **12**) (Scheme 12, Table 2) were screened (Table 2).

After these results were obtained, work concentrated on optimisation of the reaction with pivaloyl chloride to give adduct **11e**. Although the *E*:*Z* ratio was the same as for the elimination reaction of the 2,4-dimethoxybenzoyl adduct **11k**, the pivaloyl chloride was a far cheaper reagent.

(25) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Essex, 1989; pp 443−445.
(26) McCague, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1011.

From these results it became apparent that, as the reaction progressed, the *E*:*Z* ratio decreased. Two possible scenarios were proposed to account for the observation:

(1) The carboxylic acid by-product from the elimination was catalysing a competing E1 elimination mechanism.

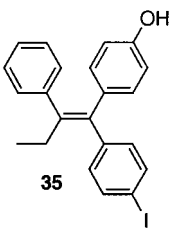
(2) The carboxylic acid by-product was isomerising the olefin after formation.

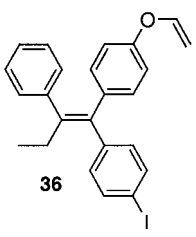
The second scenario was eliminated by refluxing geometrically pure idoxifene in xylene with acetic acid (1 equiv), no isomerisation was seen.

The reaction of the pivalate ester **11e** in refluxing xylene with 10 equiv of sodium carbonate demonstrated that the *E*:*Z* ratio was maintained (ca. 14:1), but 48 h at reflux was required for complete reaction. Other solvents and bases were then investigated. Switching solvent to 1,2,4-trimethylbenzene brought reaction times down to 16 h, although *E*:*Z* ratios were variable when using sodium carbonate. When 1,1,1,3,3,3-hexamethyldisilazane (HMDS) was employed, the *E*:*Z* ratios were reliably high (91:9 to 93.5:6.5), much more so than with other amines (Hünig's base and DBU). HMDS may well be acting as a silylating agent to form the TMS ester of pivalic acid rather than simply as a base.

Streamlining the Process. To streamline the process further we envisaged that isolation of the tertiary alcohol **12** and the pivalate ester **11e** could be avoided if the reaction solvent was changed to 1,2,4-trimethylbenzene throughout the process. Hence, the Grignard reagent **14** was formed in THF and subsequently treated with a solution of the ketone **13** in 1,2,4-trimethylbenzene. After aqueous work-up and distillation of a small amount of the solvent to remove traces of water, the solution of the crude tertiary alcohol **12** was treated with a 1,2,4-trimethylbenzene solution of KHMDS followed by pivaloyl chloride. The crude solution of ester **11e** was then washed with water and again dried by azeotropic distillation. HMDS was then added and the solution brought to reflux for 12−14 h to give complete conversion to idoxifene (*E*:*Z* ratio 93:7). Isolation of idoxifene **1** was achieved by concentration of the solution to two volumes followed by dilution with eight volumes of methanol to crystallise the product. The crude product was isolated by filtration and then recrystallised from ethanol/methanol (99:1, IMS 99%) to yield the pure product **1** in 70% yield from ketone **13**.

Direct acylation of the magnesium alkoxide of alcohol **12** with pivaloyl chloride after addition of the Grignard reagent **14** was attempted, but the reaction failed to go to completion. Conversion of the crude solution of ester **11e** to idoxifene **1** without aqueous work-up was briefly investigated, but the procedure gave higher levels of the impurities **35** and **36**.

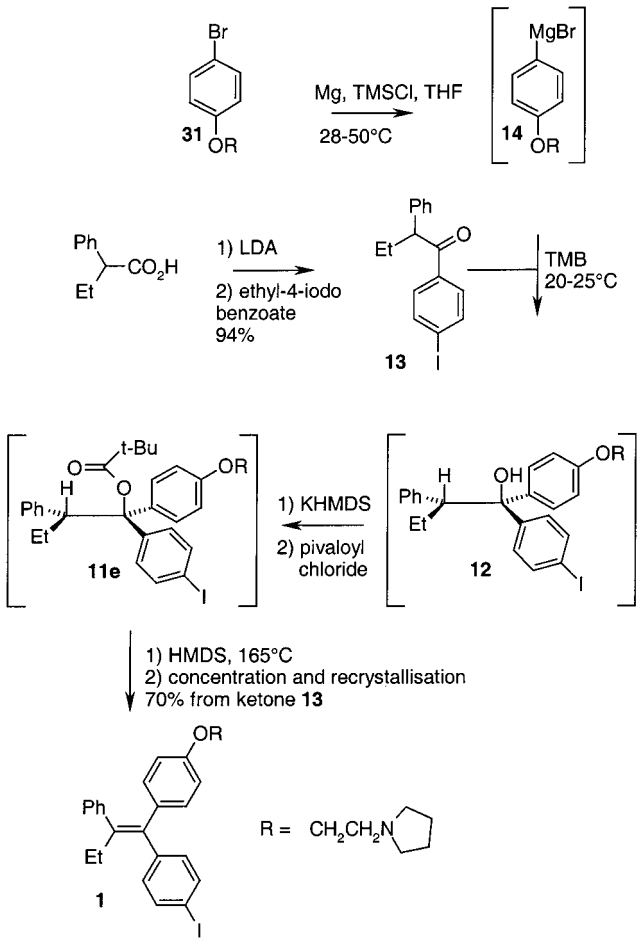




Summary

In conclusion a reliable and efficient synthesis of ketone **13** has been developed and demonstrated on scale. A route to aryl bromide **23** was developed and used to make initial multikilogram quantities before the supply was outsourced. An addition reaction of Grignard reagent **14** onto ketone **13** yielded tertiary alcohol **12** essentially as a single diastereoisomer. When alcohol **12** was derivatised as the pivalate ester **11e**, a syn-elimination reaction could be performed, yielding idoxifene **1** as a 93:7 mixture of the *E*- and *Z*-isomers. The *E*-idoxifene **1** can be obtained pure after crystallisation from methanol and recrystallisation from IMS 99% in 70% yield from ketone **13** (Scheme 13).

Scheme 13. **Manufacturing route to idoxifene**



Experimental Section

Melting points were recorded on a Buchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded in ATR mode or as a dispersion in mineral oil at 4 cm^{-1} resolution on a Nicolet 710 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C) on a JEOL GSX400 FT-NMR spectrometer. Mass spectra were recorded using CI or EI mode at an ionisation energy of 70 eV on a VG Trio-2 single quadrupole mass spectrometer; exact mass measurements were made using EI mode on a JEOL SX102 double focusing mass spectrometer. Elemental analysis was performed on a Control Equipment 440 elemental analyser.

Initial Supply Route. 2-Phenoxyethyl Chloride (4). Toluene (395 kg) was charged to a clean, dry, nitrogen-flushed vessel and the solvent heated with stirring to reflux under a Dean−Stark water separator. The contents of the vessel were then cooled to 100−105 °C before the addition of 2-phenoxyethanol **3** (70 kg, 506.6 mol) followed by pyridine (43.9 kg, 554.9 mol, 1.1 equiv), washed in with toluene (21 kg). The reaction mixture was then heated to reflux before the addition of thionyl chloride (63.5 kg, 533.8 mol, 1.05 equiv) as a solution in toluene (42 kg) over 90 min, washed in with toluene (21 kg). The reaction mixture was then heated at reflux for 1 h before being cooled to 20−25 °C. Water (490 L) was then added and the solution stirred at 20−25 °C for 10 min before settling for 15 min. The aqueous phase was then separated and discarded. The washing procedure was repeated one more time before the vessel was set for vacuum distillation and heated at less than 60 °C until toluene (500 L) had been removed. The residue was then cooled to 30−35 °C before being transferred to a smaller vessel, washed in with toluene (3.6 kg). The residue was then distilled under vacuum (10−15 mbar) at 110−120 °C to give 2-phenoxyethyl chloride[27] **4** (71.44 kg, 69.7 kg at 100%, 445 mol, 88%).

1-[4-(2-Chloroethoxy)phenyl]-2-phenyl-1-butanone (5). 2-Phenoxyethyl chloride **4** (71.7 kg, 69.94 kg at 100%, 446.6 mol) was charged to a reactor containing 1,2-dichloroethane (184.0 kg) and washed in with 1,2-dichloroethane (25.0 kg). 2-Phenylbutyric acid (74.4 kg at 98.7%, 73.4 kg at 100%, 447.0 mol) was added. The reaction mixture was adjusted to 14 °C, and trifluoroacetic anhydride (161.4 kg, 768.5 mol) was added over 46 min, maintaining the temperature at 14−18 °C and washed in with 1,2-dichloroethane (37.3 kg). The reaction mixture was stirred at 18−21 °C for 32 min and then slowly heated over 2 h to 33 °C and held at this temperature for 23 h. The reaction mixture was cooled to 23 °C, and toluene (353.0 kg) was added. A solution of sodium carbonate (86.0 kg) in demineralised water (507.0 L) was slowly added over 2.5 h, maintaining the temperature at 18−22 °C. The reaction mixture was then allowed to separate for 35 min. The lower aqueous layer was separated and discarded. The organic layer was washed with demineralised water (1 × 355.0 L) and the mixture allowed to settle before the aqueous layer was separated and discarded. Solvent (475.0 L) was distilled off at atmospheric pressure. The solution was cooled to 20 °C, and petroleum ether 80−100 (477.0 kg) added. The suspension was cooled to 5 °C and stirred at 0−5 °C for 1 h. The product was isolated by filtration and washed with cold petroleum ether (80−100) (135.0 kg). The wet product was dried in the filter drier at 15−25 °C for 30 h to give ketone[27] **5** (105.5 kg, 348.4 mol, 78%).

1-(2-{4-[(*E*)-1-(4-Iodophenyl)-2-phenyl-but-1-enyl]-phenoxy}ethyl)pyrrolidine, Idoxifene (1). Dry toluene (340.0 kg), 1,4-diiodobenzene (36.28 kg, 36.1 kg at 100%, 109.4 mol), and ketone **5** (30.0 kg, 99.1 mol) were charged to a vessel and cooled to −60 °C. *n*-Butyllithium in hexane (48.7 kg at 15.0%, 7.31 kg at 100%, 114.1 mol) was added over 2 h, maintaining the temperature between −67 and −54 °C. The mixture was stirred at this temperature for 53 min. Further butyllithium in hexane (2.0 kg at 15.0%, 0.3 kg at 100%, 4.68 mol) was added over 2 min and washed in with hexane (2.7 kg). The reaction mixture was transferred to a second vessel containing a solution of ammonium chloride (50.0 kg) in water (150.0 L) and washed in with toluene (52.0 kg), and the reaction mixture temperature was adjusted to 20 °C. The reaction mixture was stirred for 15 min and allowed to separate for 30 min. The lower aqueous phase was separated and discarded. Solvent (475 L) was distilled off at atmospheric pressure to leave an approximate volume of 120.0 L. The solution was transferred to a third vessel and washed in with toluene (20.0 kg). Solvent (75 L) was distilled off in vacuo to leave an approximate volume of 40.0 L. Ethanol (30 L) was then added and a "put and take" distillation carried out, maintaining the volume in the vessel, by the addition of ethanol (8 × 30.0 L), until an internal temperature of 80.5 °C was obtained. The ethanolic solution of tertiary alcohol **6** was then treated with ethanol (94.6 kg) and concentrated hydrochloric acid (2.5 kg). The reaction mixture was heated to reflux (78 °C) and held at reflux for 30 min. The reaction mixture was cooled to 40 °C over 30 min, and pyrrolidine (43.0 kg at 99.2%, 42.7 kg at 100%, 600.4 mol) was added. The reaction mixture was heated to reflux (83 °C) and held at reflux for 16 h. The solution of crude idoxifene **1** was filtered hot, at 70 °C, into another reactor. The transfer line was washed through with hot ethanol (4.0 kg). Idoxifene **1** seed crystals (1.0 g) were added at 51 °C. The product started to crystallise after 35 min at 28 °C. The reaction mixture was cooled to 1 °C over 30 min and stirred at 0−5 °C for 2 h. The product was isolated by centrifugation and washed with cold (5 °C) filtered ethanol (72.0 kg). The wet product **1** (24.4 kg) was added to filtered absolute ethanol (100.0 kg). The mixture was heated to reflux (78 °C) and held at reflux for 10 min to confirm that dissolution had occurred. The solution was cooled and the product crystallised at 52 °C after 13 min. The reaction mixture was cooled to 5 °C over 72 min and held at this temperature for 3 h. The product was isolated by centrifugation and washed with cold, filtered ethanol (48.0 kg). The wet product **1** (19.6 kg) was dried in a vacuum pan drier at 45−50 °C for 24 h to give, after sieving, idoxifene **1** (18.0 kg at 99.9%, 17.98 kg at 100%, 34.3 mol, 35%) as an off-white crystalline solid; mp = 106−109 °C; IR (Nujol, cm^{-1}) 3050 (m), 1604 (m), 1507 (s), 1247 (m), 1044 (m), 831 (s); ^1H NMR ($CDCl_3$, 400 MHz) 7.66 (2H, d, J = 8.4 Hz), 7.19−7.05 (5H, m), 6.98 (2H, d, J = 8.4 Hz), 6.73 (2H, d, J = 8.8 Hz), 6.55 (2H, d, J = 8.8 Hz), 3.96 (2H, t, J = 6.0 Hz), 2.81 (2H, t, J = 6.0 Hz), 2.62−2.57 (4H, m), 2.44 (2H, q, J = 7.5 Hz), 1.82−1.77 (4H, m), 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 156.9, 143.3, 142.0, 141.8, 137.2, 137.1, 134.9, 131.8, 131.5, 129.6, 127.9, 126.2, 113.4, 92.1, 66.7, 55.0, 54.7, 29.0, 23.4, 13.6; MS m/z 523 $(M)^+$ (30); HRMS calcd for $C_{28}H_{30}INO$ *m/z* 523.1372 found 523.1368; Anal. calcd for $C_{28}H_{30}INO$: C 64.25, H 5.78, N 2.68, I 24.24; found: C 64.21, H 5.76, N 2.72, I 24.27.

(27) Bell, R. A.; Dickson, K. C.; Valliant, J. F. *Can. J. Chem.* **1999**, *77*, 146.

McMurry Approach. 1-[4-(2-Chloroethoxy)phenyl]-1-(4-iodophenyl)methanone (9). To a solution of 2-phenoxyethyl chloride **4** (14.7 g, 93.9 mmol) and 4-iodobenzoyl chloride (25.0 g, 93.9 mmol) in carbon disulfide (65 mL) magnetically stirred at 25 °C under nitrogen was added aluminum chloride (10.65 g, 79.8 mmol) over 10 min; an exothermic reaction resulted in a deep red mixture. The reaction mixture was stirred at room temperature for 2 h before being poured onto ice/water/concentrated hydrochloric acid (1:1:2) (300 mL). The mixture was warmed to room temperature and the product extracted into DCM (1 × 300 mL and 1 × 125 mL). The combined organic extract was washed with water (150 mL) before being dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was recrystallised from ethyl acetate/hexane (1:2) (300 mL), affording benzophenone **9** (22.6 g, 58.2 mmol, 62%) as a pale pink crystalline solid; mp = 149 °C; IR (ATR mode, cm^{-1}) 1637 (m), 1602 (m), 1577 (m), 1253 (m), 1031 (s), 752 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.84 (2H, d, J = 6.4 Hz), 7.80 (2H, d, J = 6.8 Hz), 7.47 (2H, d, J = 6.4 Hz), 6.98 (2H, d, J = 6.4 Hz), 4.32 (3H, t, J = 5.6 Hz), 3.86 (3H, t, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 194.5, 161.9, 137.5, 132.4, 131.2, 130.3, 114.2, 99.5, 68.1, 41.6; MS *m/z* 386 $(^{35}ClM)^+$ (100), 388 $(^{37}ClM + 1)^+$ (32); HRMS calcd for $C_{15}H_{12}35ClIO_2$ *m/z* 385.9571 found 385.9569.

1-(2-{4-[(*E*)-1-(4-Iodophenyl)-2-phenylbut-1-enyl]-phenoxy}ethyl)pyrrolidine, Idoxifene (1). To a magnetically stirred mixture of zinc dust (10.67 g, 163.2 mmol), 1,2-bis(diphenylphosphino)ethane (32.0 g, 80.3 mmol), and dry 1,4-dioxane (260 mL) at room temperature under nitrogen was added titanium(IV)chloride (15.2 g, 8.80 mL, 80.3 mmol) dropwise over 15 min. The reaction mixture was then heated to reflux for 2 h before being cooled to room temperature and treated with a mixture of benzophenone **9** (10.0 g, 25.9 mmol), propiophenone (3.47 g, 3.44 mL, 25.9 mmol) in dry 1,4-dioxane (130 mL). The reaction mixture was then heated to reflux for 2.5 h before being cooled to room temperature and partitioned between DCM (500 mL) and water (200 mL). The organic layer was separated and washed with 2 M hydrochloric acid (200 mL) and then dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. The residue was extracted into boiling hexane (2 × 200 mL) and the combined organic solution filtered before being concentrated in vacuo to give crude alkene **7** (*E*:*Z* 4.1:1) as a yellow oil. The crude product was dissolved in ethanol (60 mL) and treated with pyrrolidine (11.1 g, 13 mL, 155 mmol), and the reaction mixture was heated at reflux under nitrogen for 18 h. The solution was then cooled to room temperature and concentrated in vacuo. The residue was chromatographed on silica eluting with ethyl acetate/methanol (9:1) to give crude idoxifene **1** as a yellow oil (5.5 g). The crude idoxifene **1** was then crystallised from ethanol (15 mL) to give pure idoxifene **1** (2.80 g, 5.34 mmol, 21%) as an off-white crystalline solid.

Synthesis of Ketone 13 from Weinreb Amide 15. 1-(4-Iodophenyl)-2-phenyl-1-butanone (13). 1,4-Diiodobenzene (6.99 g, 21.18 mmol) in THF (80 mL) at −78 °C, magnetically stirred under argon, was treated dropwise with a solution of *n*-butyllithium (12.6 mL of 1.6 M in hexanes, 20.22 mmol) and the resulting green suspension stirred for 30 min. In a separate flask amide **15** (3.99 g, 19.26 mmol) in THF (30 mL) was cooled to −78 °C and treated with the solution of 4-iodophenyllithium prepared above in a single portion. The reaction mixture was then stirred at −78 °C for 30 min before being warmed to room temperature and quenched by the addition of 1 M ammonium chloride solution (80 mL). The product was extracted into ether (2 × 40 mL), and the combined ethereal extracts were washed with 2 M hydrochloric acid (50 mL) followed by saturated sodium bicarbonate solution (50 mL) before being dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product **13** (6.63 g). The crude material was then recrystallised from petroleum ether (80−100) giving pure ketone **13** (3.24 g, 9.23 mmol, 48%) as a white crystalline solid; mp = 88−89 °C; IR (ATR mode, cm^{-1}) 2969 (w), 2925 (w), 1676 (s), 1577 (s), 1000 (s); ^{1}HNMR ($CDCl_3$, 400 MHz) 7.73 (2H, dt, J = 8.6, 1.9 Hz), 7.65 (2H, dt, J = 8.6, 1.9 Hz), 7.32−7.16 (5H, m), 4.34 (1H, t, J = 7.2 Hz), 2.25−2.13 (1H, m), 1.91−1.78 (1H, m), 0.88 (3H, t, J = 7.3 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz) 199.7, 139.7, 138.2, 136.6, 130.5, 129.4, 128.6, 127.5, 101.2, 55.8, 27.4, 12.7; HRMS calcd for $C_{16}H_{15}IO$ *m/z* 350.0168 found 350.0155. Anal. calcd for $C_{16}H_{15}IO$: C 54.88, H 4.32; found: C 54.80, H 4.34.

Synthesis of Ketone 13 from 4-Iodobenzoyl Chloride. 1-(4-Iodophenyl)-2-phenyl-1-butanone (13). To a stirred solution of diisopropylamine (56.4 mL, 401.9 mmol) in THF (100 mL) at 0 °C under argon was added dropwise *n*-butyllithium (240 mL of 1.6 M in hexanes, 383.7 mmol). The yellow solution was then stirred at 0 °C for 1 h before the dropwise addition of a solution of 2-phenylbutyric acid (30.0 g, 182.7 mmol) in THF (130 mL). The solution was then stirred at 0 °C for 5 min before being warmed to room temperature and stirred for a further 2 h. The solution was then cooled to −10 °C and treated dropwise with a solution of 4-iodobenzoyl chloride (48.6 g, 182.7 mmol) in THF (140 mL). The solution was then stirred at −10 °C for a further 1 h before being allowed to warm to room temperature. The reaction mixture was then quenched with 1 M ammonium chloride solution (800 mL). The product was then extracted into ether (2 × 750 mL and 1 × 300 mL). The combined organic phase was then washed with 2 M hydrochloric acid (400 mL) followed by saturated sodium bicarbonate solution (400 mL). The ethereal extract was then dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product **13** (60.9 g). The crude solid was then recrystallised from ethanol (150 mL) to give pure ketone **13** (44.76 g, 127.8 mmol, 70%) as a white crystalline solid.

Laboratory Preparation of Aryl Bromide 23. 1-[2-(4-Bromophenoxy)ethyl]pyrrolidine (23). Sodium ethoxide (70.88 g of 96%, 1.00 mol) was dissolved in ethanol (1 L) with stirring under nitrogen. A solution of 4-bromophenol (86.5 g, 0.50 mol) in ethanol (500 mL) was added in one portion, and the reaction mixture was then treated with a solution of *N*-(2-chloroethyl)pyrrolidine hydrochloride (85.04 g, 0.50 mol) in ethanol (500 mL). A precipitate formed immediately. The reaction mixture was then heated at reflux

for 60 h. Approximately half of the solvent was removed by distillation and the remainder of the reaction mixture cooled to room temperature and diluted with water (3 L). The product was extracted into ether (4 × 750 mL) and the combined ethereal extract washed with 1 M sodium hydroxide solution (2 × 750 mL) followed by brine (1 L). The organic solution was then dried ($MgSO_4$), filtered, and concentrated in vacuo to give a brown liquid (118.4 g). The liquid was distilled and a fraction (104.42 g) (bp 122−125 °C, 0.4 mmHg) collected. This fraction was distilled again to give aryl bromide[28] **23** (99.43 g, 368 mmol, 74%) (bp 139−141 °C, 1.5 mmHg) as a pale yellow oil. IR (ATR mode, cm^{-1}) 2962 (w), 2782 (w), 1487 (s), 1241 (s), 819 (m); ^1H NMR ($CDCl_3$, 400 MHz) 7.40−7.32 (2H, m), 6.82−6.75 (2H, m), 4.07 (2H, t, $J = 5.9$ Hz), 2.89 (2H, t, $J = 5.9$ Hz), 2.68−2.57 (4H, m), 1.88−1.72 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 158.0, 132.2, 116.4, 112.8, 67.3, 545.0, 54.7, 23.5; MS *m/z* 270 ($^{79}BrM + 1)^+$ (98), 272 ($^{81}BrM + 1)^+$ (100).

Pilot-Plant Preparation of Aryl Bromide 23. 1-[2-(4-Bromophenoxy)ethyl]pyrrolidine (23). 4-Methyl-2-pentanone (360.0 kg), 325 mesh potassium carbonate powder (120.0 kg), 4-bromophenol (30.0 kg at 99.6%, 29.9 kg at 100%, 172.8 mol) and *N*-(2-chloroethyl)pyrrolidine hydrochloride (29.5 kg, 173.2 mol) were charged to a vessel. The reaction mixture was heated to 87 °C over 33 min and held at 80−87 °C for 8 h. The reaction was then cooled to 20−25 °C over 46 min. Water (300.0 L) and *n*-hexane (140.0 kg) were charged, and the reaction mixture was stirred for 10 min and allowed to separate for 15 min. The aqueous layer was separated and discarded. The product was extracted from the organic phase into 2 M hydrochloric acid solution (135.0 kg). The organic phase was separated and discarded. Sodium hydroxide solution (2 M, 169.6 kg), was slowly added to the solution of product in 2 M hydrochloric acid, maintaining the temperature at 20−25 °C. *n*-Hexane (140.0 kg) was added and the mixture stirred for 5 min and allowed to separate for 15 min. The aqueous phase was separated and discarded. Zinc chloride solution (1.2 kg in water 100.0 kg) was added to the organic phase and the mixture stirred for 5 min and then filtered to remove a gelatinous precipitate. The mixture was allowed to separate, and the aqueous layer was separated and discarded. The organic phase was then washed with saturated sodium chloride solution (135.0 kg). The aqueous layer was separated and discarded. The organic phase was concentrated in vacuo and *n*-hexane (175.0 L) distilled off to leave approximately 30.0 L of oil. The oil was cooled to 20 °C over 65 min and transferred to a new, clean polydrum to give the crude product, 33.68 kg at 96.9% (GC PAR). Three batches were combined for purification, thus providing crude aryl bromide **23** (88.97 kg at 96.8%, 86.15 kg at 100%, 319mol) which was distilled at 139−143 °C, at 0.25−0.3 mbar to give the purified aryl bromide[28] **23** (82.33 kg at 98.9%, 81.43 kg at 100%, 301.6 mol, 65%) as a pale yellow oil.

Alternative Laboratory Preparation of Aryl Bromide 23. 2-(4-Bromophenoxy)ethyl Chloride (30). Toluene (50 mL) and pyridine (4.00 g, 4.1 mL, 50.6 mmol) were brought to reflux under a Dean and Stark water separator, and reflux continued for 1 h. The solution was then cooled to room temperature and treated with 2-(4-bromophenoxy)ethanol **29** (10.0 g, 46.1 mmol), and the solution was heated to reflux before the dropwise addition of thionyl chloride (5.79 g, 3.55 mL, 48.7 mmol) over 30 min. The reaction mixture was heated at reflux for 2 h before being cooled to room temperature and quenched by the addition of water (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo, affording a solid that was recrystallised from *n*-hexane to give the alkyl chloride[28] **30** (7.71 g, 32.7 mmol, 71%) as a white crystalline solid; mp 55−57 °C; IR (ATR mode, cm^{-1}) 2945 (w), 1485 (m), 1233 (m), 1033 (m), 817 (s); ^1H NMR ($CDCl_3$, 400 MHz) 7.42−7.35 (2H, m), 6.83−6.75 (2H, m), 4.20 (2H, t, $J = 5.9$ Hz), 3.80 (2H, t, $J = 5.9$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 157.7, 132.8, 117.0, 114.1, 68.7, 42.2.

1-[2-(4-Bromophenoxy)ethyl]pyrrolidine (23). 2-(4-Bromophenoxy)ethyl chloride **30** (5.0 g, 21.2 mmol), pyrrolidine (7.55 g, 8.9 mL, 106.2 mmol) and ethanol (30 mL) were heated at reflux under nitrogen for 18 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was dissolved in water (50 mL) and the pH adjusted to 12 by the addition of 40% w/v sodium hydroxide solution. The product was then extracted into hexane (2 × 50 mL). The combined organic extract was dried by filtration through phase-separation paper and concentrated in vacuo to give a red oil (5.36 g) that was Kugelrohr distilled (ot 175 °C, 0.1 mbar) to give aryl bromide[28] **23** (5.10 g, 18.9 mmol, 89%) as a clear colourless oil.

Laboratory Preparation of Tertiary Alcohol 12. (1*RS*,2*SR*)-1-(4-Iodophenyl)-2-phenyl-1-[4-(2-pyrrolidin-1-ylethoxy)phenyl]butan-1-ol (12). Approximately 20 mL of a solution of aryl bromide **23** (40.0 g, 0.148 mol) and 1,2-dibromoethane (6.4 mL, 74 mmol) in dry THF (300 mL) was added to a mixture of magnesium raspings (5.94 g, 0.244 mol) in THF (50 mL) and magnetically stirred at room temperature under nitrogen. The reaction mixture was then heated to 50 °C at which point a visible reaction took place. Once the reaction had subsided, the reaction mixture was heated to reflux, the remainder of the aryl bromide **23** solution was added over 2 h, and the reaction mixture was heated at reflux for a further 30 min. The reaction mixture was then cooled to room temperature, and the concentration of the Grignard reagent **14** solution was ascertained by titration with 2-butanol in *p*-xylene using 1,10-phenanthroline as an indicator. Ketone **13** (40.0 g, 0.114 mol) in THF (100 mL) was then added dropwise over 30 min, maintaining the reaction temperature at ca. 25 °C with a cold water bath. After the addition the reaction mixture was stirred for a further 30 min before being poured onto a mixture of crushed ice (600 g) and 1 M aqueous ammonium chloride solution (1.2 L). The crude product was extracted into ether (3 × 800 mL), and the combined organic phases were washed with brine (1 L), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude tertiary alcohol **12** (71.38 g). The crude product was slurried in petroleum ether (60−80)/

(28) Reagent available from Sigma-Aldrich, Ltd.

toluene (9:1) (250 mL) for 1 h before isolation by filtration and drying in a desiccator at 1 mmHg to give the tertiary alcohol **12** (54.44 g, 0.101 mol, 88%) as an off-white solid; mp = 120−123 °C; IR (ATR mode, cm^{-1}) 3102 (w), 2964 (w), 2827 (w), 1507 (m), 1480 (m), 1248 (s), 1178 (m); ^{1}-HNMR ($CDCl_3$, 400 MHz) 7.45−7.40 (2H,m), 7.40−7.35 (2H, m), 7.17−7.06 (5H, m), 6.94−6.86 (4H, m), 4.09 (2H, t, J = 6.1 Hz), 3.48 (1H,. dd, J = 6.1, 4.0 Hz), 2.89 (2H, t, J = 6.1 Hz), 2.67−2.58 (4H, m), 2.37 (1H, br s), 1.88−1.72 (6H,m), 0.75 (3H, t, J = 7.3 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz) 155.8, 144.8, 137.7, 136.1, 134.6, 128.2, 126.0, 125.9, 125.4, 125.6, 112.4, 89.8, 78.6, 65.1, 54.2, 53.2, 52.8, 21.6, 21.5, 10.7; MS *m/z* 542 $(M + 1)^+$ (100); HRMS calcd for $C_{28}H_{32}NIO_2$ *m/z* 541.1478, found 541.1467.

Manufacturing Route. 1-(4-Iodophenyl)-2-phenyl-1-butanone (13). Dry THF (11.0 kg) and lithium diisopropylamide in heptane/ethylbenzene/THF (183.5 kg at 25.2%, 46.2 kg at 100%, 431.3 mol) were charged to a vessel and washed in with dry THF (4.0 kg). A solution of 2-phenylbutyric acid (35.9 kg, 218.7 mol) in dry THF (65 kg) was added over 85 min, maintaining the temperature at 23−24 °C and washed in with dry THF (30 kg). The reaction mixture was stirred at 10−20 °C for 1.5 h. The solution of dianion **16** was added over 30 min to a solution of ethyl 4-iodobenzoate **18** (48.4 kg, 175.3 mol) in toluene (156.4 kg) and washed in with dry THF (30 kg). The reaction mixture was stirred at 20−23 °C for 1 h. The reaction mixture was quenched into concentrated hydrochloric acid (110 kg) in water (140.0 L) over 1 h, maintaining the temperature between 17 and 27 °C, and washed in with toluene (30 kg). The reaction mixture was then stirred for 5 min before the phases were allowed to separate for 45 min. The lower aqueous phase was separated and discarded. A solution of sodium carbonate (24.5 kg) in water (195 L) was charged, the reaction mixture was stirred for 5 min, and the phases were allowed to separate for 25 min. The lower aqueous phase was separated and discarded. Water (170 L) was charged, the reaction mixture was stirred for 5 min, and the phases were allowed to separate for 15 min. The lower aqueous phase was separated and discarded. The organic layer was transferred to another vessel and washed in with toluene (10 kg). Solvent (450 L) was distilled off in vacuo to leave ca. 70 L of solution. *iso*-Propanol (192 kg) was added, the solution was heated to 59 °C, and complete dissolution was confirmed. The reaction mixture was then cooled to 0 °C over 3.5 h to cause crystallisation and then stirred at 0 °C for 1 h. The product **13** was then isolated by filtration and washed with cold 2-propanol (77 kg). The wet product was then dried in vacuo at 25−30 °C for 24 h to give the pure ketone **13** (57.5 kg, 164.2 mol, 94%) as a white crystalline solid.

1-(2-{4-[(*E*)-1-(4-Iodophenyl)-2-phenylbut-1-enyl]-phenoxy}ethyl)pyrrolidine, Idoxifene (1). To a thoroughly nitrogen-purged vessel was added THF (100 kg) and magnesium raspings (4.8 kg, 197.5 mol), and the mixture was stirred at 25−28 °C before the addition of a 1.0 M solution of TMSCl in THF (3.6 kg, 4.1 L, 4.1 mol of TMSCl) washed in with THF (2 kg). The mixture was stirred for 10 min. A separate nitrogen-purged vessel was charged with aryl bromide **23** (45 kg, 166.6 mol) and THF (100 kg) and stirred at 20−25 °C to ensure homogeneity; 15 L of the aryl bromide **23** solution was then added to the suspension of activated magesium raspings in THF. The reaction mixture was then stirred until initiation occurred, apparent by an internal temperature rise to ca. 50 °C (time taken to initiate was between 5 and 40 min, depending on the quality of the THF). The remainder of the aryl bromide **23** solution was then added over 45 min, maintaining the temperature between 38 and 51 °C. The aryl bromide **23** solution was then washed in with THF (25 kg). The solution of Grignard reagent **14** was then stirred at 45−50 °C for 30 min before being cooled to 20−25 °C. The concentration of the Grignard reagent **14** solution was then determined by on-line IR spectroscopy using the React-IR system or by titration of a sample from the vessel with *s*-BuOH in *p*-xylene using 1,10-phenanthroline as an indicator.[25] The solution of Grignard reagent **14** was then filtered into a clean, dry, nitrogen-purged vessel and washed in with THF (25 kg). To the Grignard reagent **14** at 20−25 °C was added a solution of ketone **13** (45 kg, 128.5 mol) in 1,2,4-trimethylbenzene (234 kg) over 1 h, maintaining the temperature at 20−25 °C, and washed in with 1,2,4-trimethylbenzene (25 kg); the reaction mixture stirred for a further 1 h 15 min at 20−25 °C. The solution was then added to a stirred solution of trisodium citrate trihydrate (74 kg) in water (340 L), maintaining the temperature at 20−25 °C, and washed in with 1,2,4-trimethylbenzene (25 kg). The biphasic mixture was stirred for 30 min and allowed to settle for 15 min before the aqueous phase was separated and discarded. The organic phase was then washed twice with water (280 L) each with a 5-min stir period and a 15-min settling period. The remaining organic phase was then concentrated in vacuo to remove residual water and THF (160 L). The solution of crude tertiary alcohol **12** was then cooled to 15−20 °C and the resulting suspension treated with a solution of KHMDS in 1,2,4-trimethylbenzene (196 kg of 17% w/w, 33.3 kg of KHMDS, 167.0 mol, 1.3 equiv) over 1 h, maintaining a temperature of 20−25 °C and washed in with 1,2,4-trimethylbenzene (25 kg). The reaction mixture was then stirred for 1 h at 20−25 °C before the addition of pivaloyl chloride solution (21.7 kg, 180.0 mol, 1.4 equiv, in 1,2,4-trimethylbenzene (40 kg)) over 1.5 h, maintaining the temperature below 30 °C, and washed in with 1,2,4-trimethylbenzene (9 kg). The solution was then stirred at 20−25 °C for 1.5 h before being washed with water (230 L) three times. Each wash was stirred for 5 min and allowed to settle for 15 min before separation. The vessel was then set for distillation, and the reaction mixture was concentrated in vacuo by distilling out 200 L of solvent. The solution of crude ester **11e** was then cooled to 80−90 °C and treated with HMDS (31.2 kg, 192.2 mol); the reaction mixture was then brought to reflux (165 °C) for 12 h. The solution was then cooled to 20−25 °C and treated with a solution of sodium carbonate (29.8 kg, 278.5 mol) in water (280 L) and the biphasic mixture stirred for 5 min and allowed to settle for 15 min before the aqueous layer was separated and

discarded. The organic phase was then washed twice with water (230 L), each wash being stirred for 5 min and allowed to settle for 15 min before being separated and discarded. The organic solution of idoxifene **1** was then concentrated in vacuo to ca. 90 L in volume and cooled to 55−60 °C before being treated with methanol (292 kg). The solution was then heated to 60−65 °C and filtered into another vessel and washed in with methanol (64 kg) where the reaction mixture was cooled to 25 °C to crystallise and then cooled further to −10 to −5 °C and the slurry stirred for 1 h. The product was isolated by filtration at −10 to −5 °C and washed with cold methanol (71 kg) and blown dry at 1.5 bar. The solid idoxifene **1** was then partially dried at 45−50 °C in vacuo for 1.5 h. The partially dried idoxifene **1** (67.8 kg) in a nitrogen-purged vessel was then treated with IMS 99% (235 kg) and heated to 65−70 °C until dissolution. The solution was then filtered into another vessel and washed in with hot IMS 99% (39 kg). The solution was then cooled to crystallise and then further to 0 °C and stirred for 1 h. The idoxifene **1** was then isolated by filtration and washed with cold IMS 99% (28.5 kg) and blown dry at 1.5 bar and then dried in vacuo at 45−50 °C to give pure idoxifene **1** (47.1 kg, 90.0 mol, 70%) as an off-white crystalline solid.

Isolation of a Pure Sample of Pivalate Ester 11e. 2,2-Dimethylpropionic Acid (1*RS*,2*SR*)-1-(4-Iodophenyl)-2-phenyl-1-[4-(2-pyrrolidin-1-ylethoxy)phenyl]butyl Ester (11e). Ester **11e** could be isolated from large-scale pilot plant work in the following manner. A solution of the pivalate ester **11e** in 1,2,4-trimethylbenzene (500 mL) obtained from the pilot plant after aqueous work-up and azeotropic drying was concentrated in vacuo (ca. 1 mmHg at 60 °C) to afford crude ester **11e** as a thick orange/brown oil (140 g). The crude material was chromatographed on silica (870 g) eluting with toluene/triethylamine (30:1) to give ester **11e** (21.2 g) as a pale yellow foam. This material was rechromatographed on silica (860 g) eluting with toluene/triethylamine (25:1) to afford pivalate ester **11e** (16.9 g, 27.0 mmol) as an off-white granular solid; mp = 69−70 °C; IR (ATR mode, cm^{-1}) 2965 (w), 2777 (w), 1727 (s), 1281 (s), 1146 (s), 815 (s); ^1H NMR ($CDCl_3$, 400 MHz) 7.65−7.6 (2H, m), 7.22−7.10 (5H, m), 6.93−6.87 (2H, m), 6.82−6.72 (4H, m), 4.44 (1H, dd, J = 12.1, 1.9 Hz), 4.12 (2H, t, J = 6.7 Hz), 2.92 (2H, t, J = 6.7 Hz), 2.70−2.58 (4H, m), 2.02−1.90 (1H, m), 1.88−1.76 (4H, m), 1.32−1.08 (1H, m), 0.88 (9H, s), 0.72 (3H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.3, 158.5, 144.2, 139.3, 137.0, 133.7, 131.1, 131.0, 130.6, 127.7, 127.2, 113.0, 93.9, 88.5, 67.5, 55.6, 55.2, 51.3, 39.6, 27.1, 26.2, 23.9, 12.7; MS *m/z* 626 $(M + 1)^+$ (100), 524 (5).

Acknowledgment

We thank John Lewis for the pilot plant support and Jeff Richards, Kevin Sutcliffe, and Mike Kingswood for the analytical support they provided during this project.

Received for review May 11, 2001.

OP0100394