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Novel Approaches towards the LTD_4/E_4 Antagonist, LY290154

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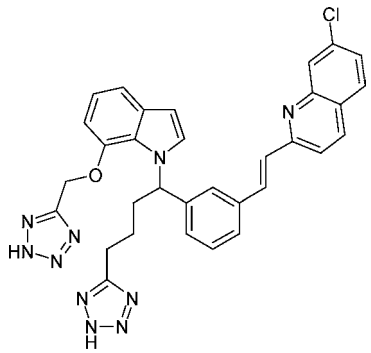
Abstract:

Several novel approaches have been investigated for the synthesis of the LTD_4/E_4 antagonist LY290154. Significant improvements to the discovery route were first made by using an indoline nucleophile instead of an indolyl anion in the key substitution step. An alternative approach, introducing the 7-chloroquinoline moiety in the latest stages of the synthesis was then demonstrated. Interestingly, the pivotal intermediate of this latter route was also obtained in a one-pot process following a Katritzky methodology. Finally, an asymmetric synthesis offering significant advantages over the enantioselective route reported by McKillop was demonstrated.



LY290154

Figure 1. **LTD_4/E_4 antagonist LY290154.**

Introduction

Asthma is the most frequently encountered allergic pulmonary disease, affecting approximately 5% of the population. It is known that asthma attacks are caused by production of slow reacting substance (SRS), triggered by pollen or other allergens, leading to constriction of air passages. It has also long been known that the major SRS component in human lung is leukotriene D_4 (LTD_4). Therefore, an extensive search for selective leukotriene receptor antagonists has been conducted. Compound LY290154 is the last drug candidate in a long series of compounds synthesized and evaluated by Lilly-Discovery for the search of a new LTD_4/E_4 antagonist (Figure 1).

Despite its excellent pharmacological profile, development of LY290154 as a suitable drug candidate, suffers from some major issues primarily related to its chemistry. For instance, the discovery route (Scheme 1) represents a very attractive pathway that is convergent at the penultimate reaction step.[1] However, the critical coupling between indole **8** and benzyl chloride **5** yields only 15% of the expected substitution product **9**. In fact, the main product of the convergent step comes from an unwanted elimination reaction leading to the by-product **11**. In addition to the extremely low overall yield of the synthesis (<2%), the formation of large amounts of by-products (Figure 2) including double-condensation product **3′** (Step 1), pinacol **4′** (Step 2), and elimination **11** (Steps 3 and 4) severely complicates the control strategy. Although the initial strategy of the program team was to develop a racemic compound, it was also highly desirable to develop a new route that could be easily amendable to an asymmetric synthesis at a later date. Alternatively, because of the very high potency of the compound (microgram daily dosage in human) and subsequent low material request, the active enantiomer can eventually be obtained by a chiral chromatography separation.

Results and Discussion

Development of the Discovery Route. The original synthetic route used by Discovery was initially improved to deliver LY290154 for preclinical toxicology studies.[2] The stoichiometry of the first step was optimized, and a 63% yield of **3** was obtained using 1.5 equiv of isophthalaldehyde (**1**) and 2.6 equiv of Ac_2O in toluene (ca. 1 M) under reflux for 12 h.[3] The level of **3′** remained higher than 20 mol % but was easily removed by filtration after dissolution of the crude **3** in boiling dichloromethane.

We prepared 3-cyanopropylzinc iodide from the corresponding iodide, zinc powder, and catalytic 1,2-dibromoethane in dry THF at 50 °C for 15 h.[4] Preactivation of zinc by 10% aqueous HCl followed by an organic wash and drying appeared critical. This was added to aldehyde **3** in the presence of $TiCl_4$ (1 equiv) affording benzyl alcohol **4** in up to 71% isolated yield. During our studies, we found ultrasonic activation allows higher yields while decreasing the level of **4′** by up to 5 mol %. Unfortunately, this result

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† This paper is dedicated to the memory of Freddy Napora.

(1) Gilmore, J.; Todd, A. Eur. Pat. Appl. EP469833, 1992.

(2) Brennan, J.; Dobson, D.; Gilmore, J.; Gorissen, H. J.; Huff, B.; Journee, G.; Kennedy, J. H.; Sawyer, J. S.; Todd, A.; Weigel, L. O. Lilly Research Laboratories. Presented at 209th ACS National Meeting, April 2, 1995, Anaheim, CA; American Chemical Society: Washington, DC, 1995.

(3) (a) Young, R. N.; Senneville, R.; Longueil, Z.; Leger, S.; Ormeaux, D. U. S. Patent 4,851,409, 1989. (b) McNamara, J. M.; Leazer, J. L.; Bhupathy, M.; Amota, J. S.; Reamer, R. A.; Reider, P. J.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3718.

(4) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Knochel, P.; Xiao, C.; Yeh, M. C. P. *Tetrahedron Lett.* **1988**, *29*, 6697. (c) Presently commercially available from Aldrich.

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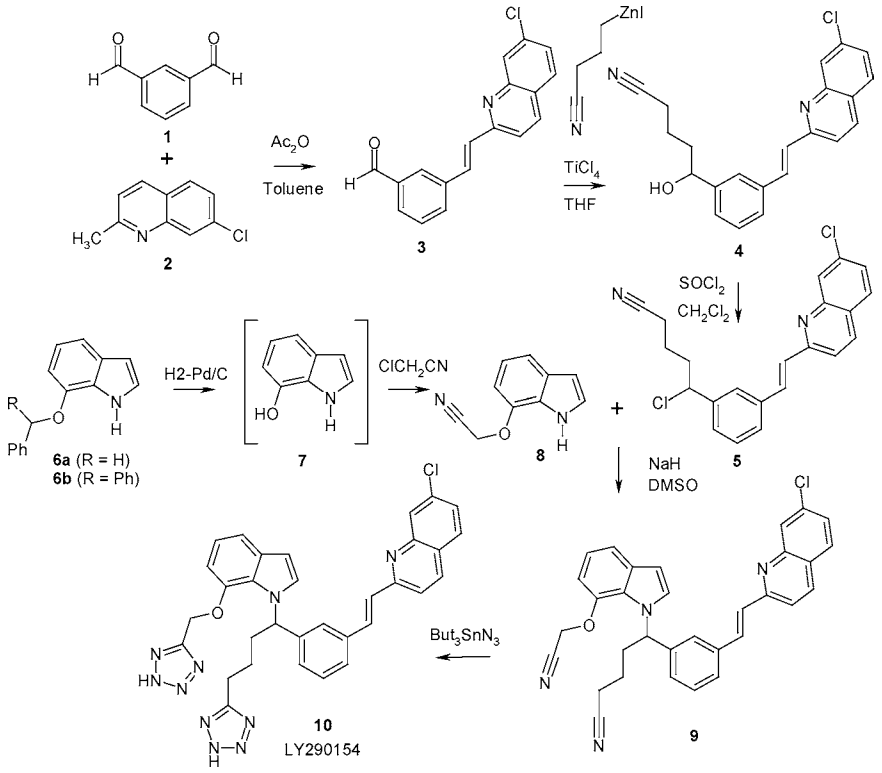
Scheme 1. **Discovery synthesis of LY290154**



could not be reproduced at larger scale. Alcohol **4** was purified via crystallization of the corresponding hydrochloride salt in ethyl acetate, thus removing unreacted **3**. This was followed by dissolution of **4**·HCl in 95% ethanol to remove the insoluble by-product **4′** by filtration. Pure **4** was finally obtained in 80% yield by crystallization after addition of acetone to the filtrate (final ratio 95% ethanol/acetone = 2:1). The benzylic chloride **5** was initially prepared by the reaction of **4** with 2 equiv of $SOCl_2$ in dichloromethane at 20 °C. Under these conditions, up to 20 mol % of elimination by-product **11** was formed. We were able to lower the amount of **11** down to 3 mol % using the NCS/PPh_3 method.[5] Workup and purification procedures for this step were also significantly improved allowing better control of the purity of **5** while avoiding a tedious chromatographic method.

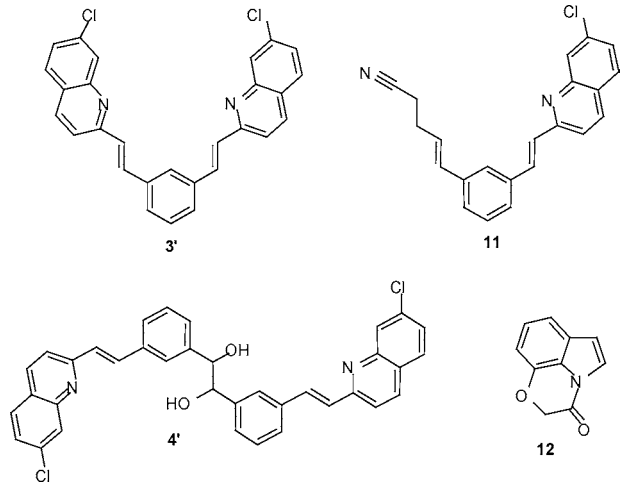


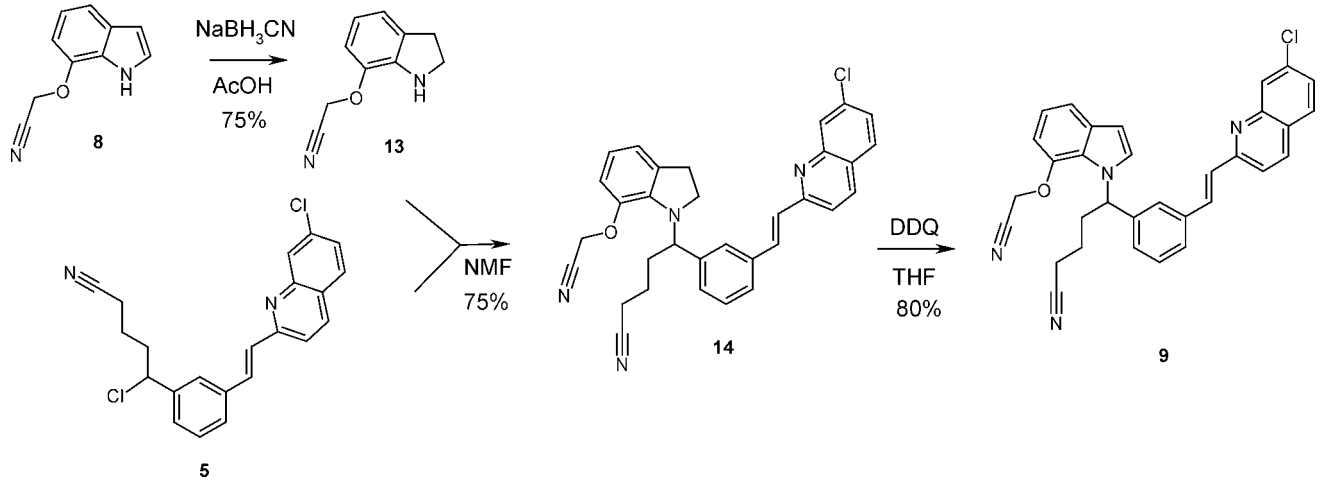
Figure 2. **Major by-products of the discovery route.**

The key issue of the original synthesis was nucleophilic substitution of **5** by anions of 7-cyanomethoxyindole **8**.[6] Despite numerous studies this step always resulted in the formation of 80 to 85 mol % of elimination by-product **11**. Large amounts of the tricyclic impurity **12** were also formed by competitive cyclization of the indolyl anion. Obviously, subsequent chromatographic purification of the penultimate intermediate **9** remained extremely tedious.[7] We reevaluated our choice of solvent (THF, NMP ≪ DMF < DMSO), counterion ($Li^+ \ll Na^+ \approx K^+$), and temperature (20−50 °C), finally obtaining a low but reproducible 30% yield using 1.5 equiv of **8** and NaH in DMSO at 25 °C for 24 h. We also improved the purification of the penultimate compound **9** by crystallizing it as its oxalate salt in a 1:1 2-propanol/ethyl acetate mixture. It was later established that this purification method was crucial to obtain highly pure LY290154. The final tetrazolation of bis-nitrile **9** was achieved in 81% yield with tributyltinazide at 120 °C for 8 h.[8] As mentioned above, high purity of starting material **9** was found to be critical for the success of this final step.

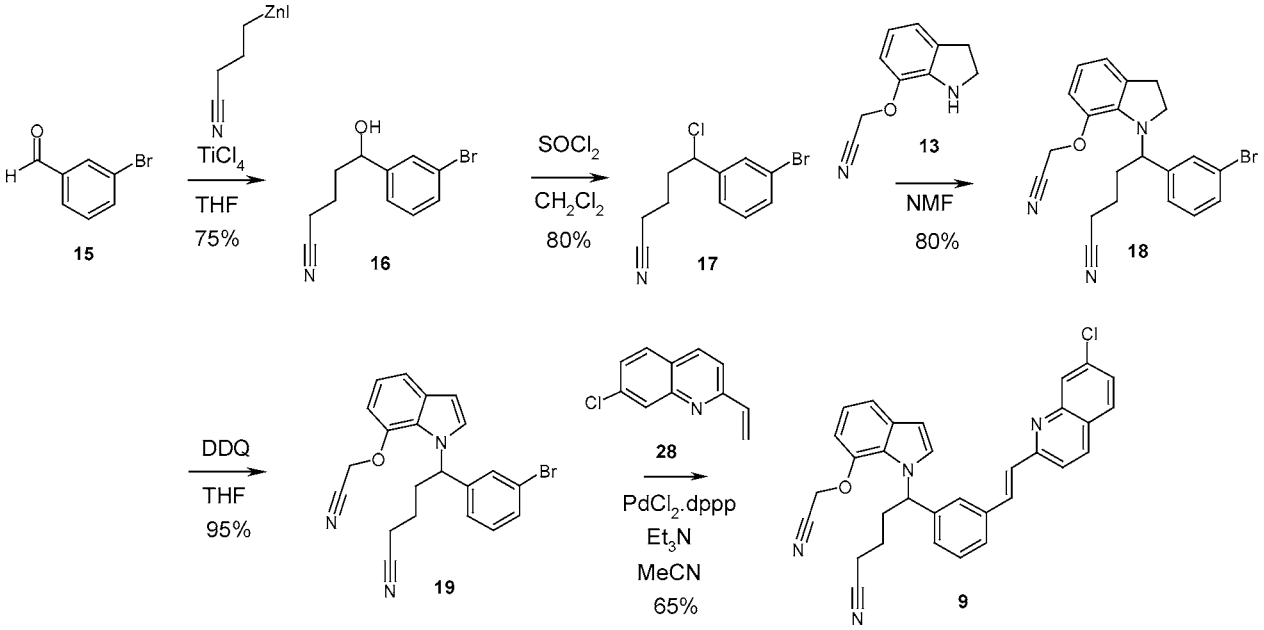
Novel Racemic Approaches. As evidenced above, there were several key issues to be considered before envisaging a scale-up of the process. Particularly, the productivity of the key convergent step of benzylic chloride **5** with indole **8** remained dramatically low. Assuming that the high basicity of the alkali metals anions derived from indole **8** ($pK_a \approx 16-17$) was the main cause of the elimination side-reaction,

(5) Bose, A. K.; Lal, B. *Tetrahedron. Lett.* **1973**, *14*, 3937.
(6) Cyanomethoxyindole can be purchased from Biosynth A.G. For a preparative method, see: Dobson, D.; Todd, A.; Gilomore, J. *Synth. Commun.* **1991**, *21*, 611.
(7) Typically required SG filtration + 2 Waters PHPLC-2000 chromatographic purifications.
(8) Huff, B. E.; Staszak, M. A. *Tetrahedron Lett*, **1993**, *34*, 8011.

Scheme 2. **Alternative indoline-based route to racemic LY290154**



Scheme 3. **Alternative Heck-based route to racemic LY290154**



we sought to utilize the corresponding indoline derivative **13** (pK_a ~4−5) as a nucleophile in the convergent step (Scheme 2). Compound **13** was obtained in 75% yield by reduction of 7-cyanomethoxyindole with sodium cyanoborohydride in acetic acid.[9]

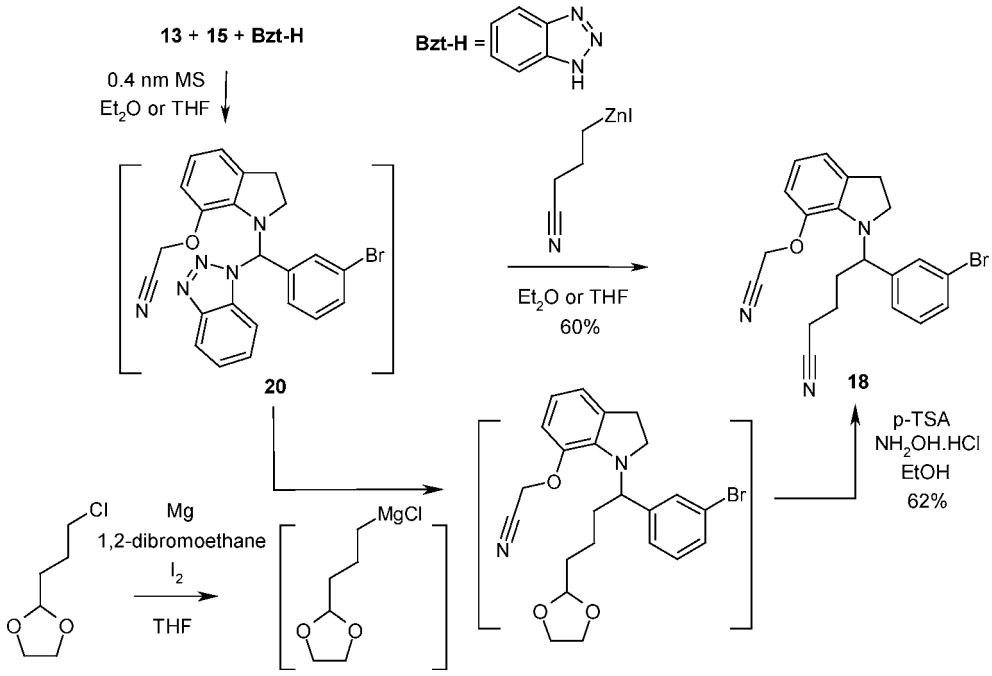
Initially, we carried out reaction of indoline **13** with the benzylic chloride **5** in classical S_N2 solvents (DMSO, DMF, acetonitrile) in the presence of various bases (Et_3N, K_2CO_3). Under these conditions incomplete conversion was obtained, even after prolonged heating (acetonitrile < DMF < DMSO), and extensive by-products were formed. Faster and cleaner reactions were obtained using *N*-methylformamide as solvent. After optimization, a 75% yield was obtained using 1.5 equiv of **13** at 50 °C for 48 h. Similar rate-enhancements of S_N2 reactions have been reported in the weakly protic solvent *N*-methylformamide in agreement with a termolecular "push−pull" mechanism.[10−11] Finally, aromatization of indoline **14** was achieved in 80% yield using DDQ in THF at 20 °C for 20 h.[12]

We then envisaged a different route aiming to introduce the chloroquinoline moiety at the end of the synthesis via a Heck coupling (Scheme 3).

This approach offers several advantages, namely the opportunity to perform an optical resolution at an earlier stage of the synthesis and avoidance of the double-condensation by-product in the first step. Interestingly, we were able to transpose to this new route most of the key findings made earlier. Thus, a 46% overall yield was obtained for the synthesis of indole **19** from 3-bromobenzaldehyde **15**. As reported by McKillop, the Heck reaction between bromide **19** and 7-chloro-2-vinyl-quinoline **28** affords the known penultimate compound **9** in 65% yield.[13]

(9) Kumar, Y.; Florvall, L. *Synth. Commun.* **1973**, *13*, 489.
(10) Ballistreri, F. P.; Maccarone, E.; Musumarra, G.; Tomaselli, G. A. *J. Org. Chem.* **1977**, *42*, 1415.
(11) (a) Swain, C. G. *J. Am. Chem. Soc.* **1948**, *70*, 1119. (b) Swain, C. G.; Eddy, R. W. *J. Am. Chem. Soc.* **1948**, *70*, 2989. (c) Swain, C. G.; Langsdorf, W. P. *J. Am. Chem. Soc.* **1951**, *73*, 2813. (d) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141. (e) Swain, C. G.; Mosely, R. B.; Bown, D. E. *J. Am. Chem. Soc.* **1955**, *77*, 3731.
(12) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153.

Scheme 4. **Katritzky approach to indoline 18**



In parallel to the laboratory development of this new route an alternate convergent approach was investigated. This led to the formation of indoline **18** in a single step from 3-bromobenzaldehyde **15**, indoline **13**, and 3-cyanopropylzinc iodide (Scheme 4) following the method reported by Katritzky.[14]

With a slight modification of the conditions reported by Katritzky, indoline **13** was reacted with 3-bromobenzaldehyde **15** and 1H-benzotriazole affording the adduct **20**. This was then converted into **18** in 60% overall yield by treatment with 3-cyanopropylzinc iodide. Alternatively, **18** is also accessible in similar yield by reaction of the adduct **20** with the Grignard reagent prepared from 2-(3-chloropropyl)-1,3-dioxolane followed by direct conversion of the protected aldehyde into the nitrile **18**.[15]

Asymmetric Synthesis. Despite screening with several chiral acids we were unable to achieve the optical resolution of racemic compounds **14** and **18** by crystallization of diastereomeric salts. In most cases, oils or amorphous solids were obtained. We assume that our difficulties forming crystalline salts is due to the weak basicity of the indoline nitrogen combined with an excessive steric constraint around the chiral centre. In the course of our investigations we have developed a powerful chromatographic separation for indoline **18** that could eventually be used to supply enough material.

Alternatively, the important breakthroughs obtained with indoline **13** as nucleophile allowed us to design an efficient and probably more scalable asymmetric synthesis (Scheme 5).[16] The key step of this approach is the asymmetric reduction of the benzylic ketone **21**. This ketone was obtained in 63% yield by Swern oxidation of the alcohol **16**.[17]

Asymmetric reduction of the ketone **21** was initially achieved using 10 mol % of the chiral oxazaborolidine **26** derived from (*S*)-(−)-diphenylprolinol.[18] Under these conditions, we obtained an 88:12 ratio (76% ee) for the chiral alcohol **22a**. A better enantioselectivity (84% ee) was obtained with Noyori's RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-mesitylene)-catalyst **27**.[19] Obviously, the (1*R*,2*R*)-Ru-catalyst would have been used to obtain the target (*R*)-alcohol **22a**, but the development of LY290154 was stopped at that time. The enantiomeric excesses of alcohols **22** were determined by ^{1}H NMR on the Mosher's ester derivatives.[20] The subsequent S_N2 chlorination step was carried out using the NCS−PPh_3 procedure developed before for the racemic synthesis to yield the chiral chloride **23** in 66% yield. No analytical method was available for ee determination on **23**. Therefore, we carried out the next step and measured the optical purity on indoline **24**. An 84:16 enantiomeric ratio was obtained by chiral LC, indicating that only minor racemisation occurred during the chlorination and/or substitution steps, probably through competitive S_N1 reaction. Aromatization of **24** with DDQ afforded the chiral indole **25** in 80% yield.

(13) Bach, N. J.; Baker, S. R.; Gilmore, J.; Lewthwaite, R. A.; McKillop, A.; Sawyer, J. S.; Stephenson, G. R.; Urquhart, M. W. J. Eur. Pat Appl. EP 0775694 A2, 1997; *Chem. Abstr.* 127: 81355. For a preparation of 7-chloro-2-vinyl-quinoline, see: Larsen, R. D.; Corley, E. G.; King, A. O.; Caroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 3398.

(14) (a) Katritzky, A. R.; Lan, X.; Fan, W. Q. *Synthesis* **1994**, 445. (b) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683 and references therein.

(15) Yamauchi, M. *Chem. Pharm. Bull.* **1993**, *41*, 2042.

(16) A 12-step asymmetric synthesis (2.4% overall yield) was also developed. See ref 13 and Montalban, A. G. Ph.D. Thesis, University of East Anglia, Norwich, 1995. The key results of this work were presented by Prof. McKillop at the ChiRex Technical Symposium, Newcastle, June 27, 1996.

(17) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(18) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen. C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(19) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.

(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme 5. **Asymmetric synthesis of LY290154**

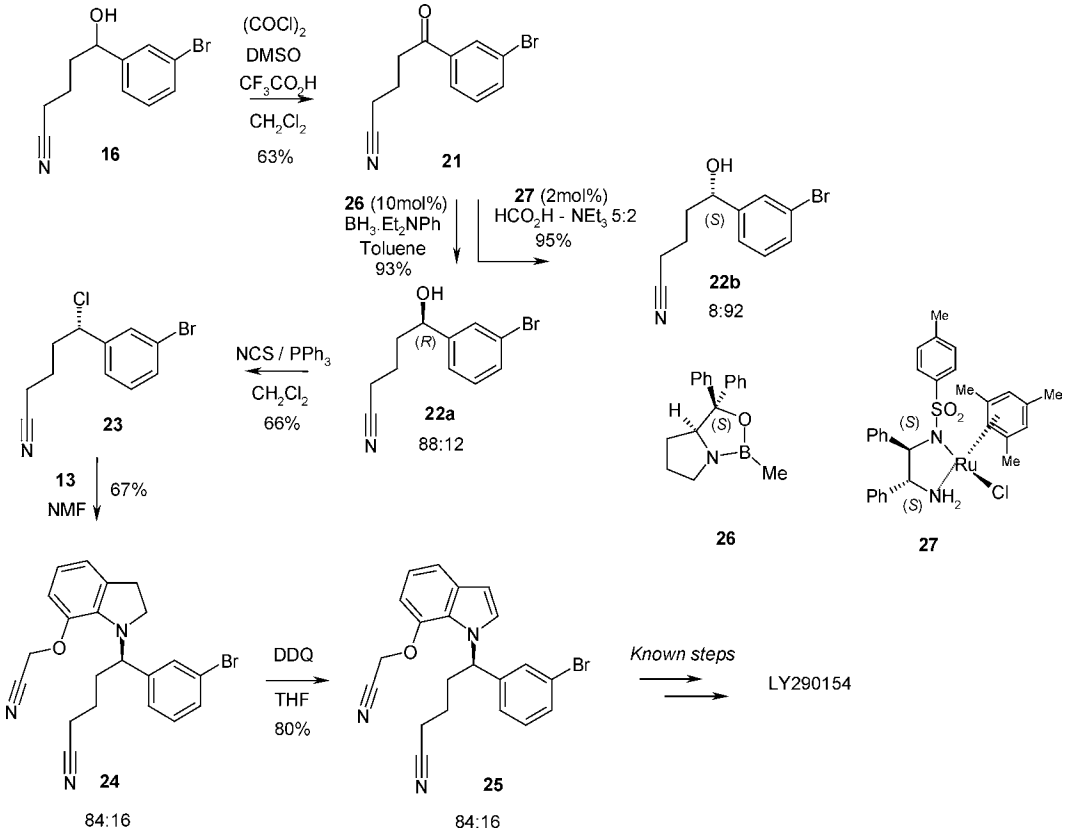


Table 1. **Comparison of the different routes**

route	total steps	LLS steps	yield (%)	resolution potential	pure *S* (max yield %)
discovery	6	5	4	no	2
indoline	7	6	10	yes (**14**)	5
Heck	7	6	16	yes (**18**)	8
Katritzky	5	5	25	yes (**18**)	12.5
asymmetric	9	8	10	–	8
McKillop	12	12	2.5	–	1.8

Summary

Having made significant improvements to the original discovery route to deliver API for preclinical toxicology studies, we have investigated several novel approaches for the synthesis of the LTD_4/E_4 antagonist LY290154. Key improvements were obtained using the indoline **13** as nucleophile in the substitution step instead of the corresponding indolyl anion. In this step we evidenced the superiority of *N*-methylformamide over classical S_N2 solvents. We have also evaluated another disconnection, introducing the 7-chloroquinoline moiety in the latest stages of the synthesis via a Heck coupling reaction. Interestingly, the key intermediate **18** of this latter approach can be obtained in a one-pot process from indoline **13**, 3-bromobenzaldehyde **15**, and 3-cyanopropylzinc iodide. Finally, we have demonstrated a novel asymmetric synthesis offering several significant advantages over the pioneer enantioselective route reported by Mc Killop.

Comparison on the Different Approaches. Table 1 summarizes the different approaches that have been evaluated for the preparation of LY290154. Considering the very high potency of the compound and the subsequent relatively small-scale production that would have been necessary per year, it is reasonable to say that a racemic approach such as the Katritzky route combined with a chiral separation could be preferred over our asymmetric synthesis.

Experimental Section

Unless specified otherwise, all reagents and solvents were used as supplied by the manufacturer. All reactions were conducted under an inert N_2 or Ar atmosphere. Melting points are uncorrected. NMR spectra (250 MHz) were recorded in $CDCl_3$ or $(CD_3)_2SO$ solutions.

(*E*)-3-[2-(7-Chloro-2-quinolinyl)ethenyl]-benzaldehyde 3. Prepared as described in *Eur. Pat. Appl.* EP469833 A1 (1992). The HPLC retention time and ^1H NMR spectrum were identical to those of a reference sample.

(*E*)-3-[2-(7-Chloro-2-quinolinyl)ethenyl]-*δ*-hydroxybenzenepentanenitrile 4. Prepared as described in *Eur. Pat. Appl.* 0469833 A1 (1992), but the purification method was improved. A typical procedure is as follows:

Crude **4** (39 g, 0.075 mol, corrected for purity) was suspended in CH_2Cl_2 (500 mL), and an aqueous saturated sodium bicarbonate solution (270 mL) was added. After being stirred for 1 h, the organic layer was separated and concentrated to dryness. The residue was dissolved in ethyl acetate (250 mL), then water (33 mL) and sodium bisulfite (7.5 g) were added under stirring. The suspension was heated at 50 °C to improve dissolution. The reaction mixture was cooled to ambient temperature, left for 12 h at ambient, and then filtered. The filtrate was washed with aqueous saturated sodium bicarbonate solution (150 mL) and brine (150 mL),

dried ($MgSO_4$, 10 g), and then filtered. The solution was further diluted with ethyl acetate (150 mL), and dry HCl in diethyl ether (20 mL, 0.072 mol) was added dropwise under stirring. After 1 h the suspension was filtered. The crystals were washed with 2-propanol (20 mL) and dried under vacuum at 40 °C for 12 h to afford 20 g of **4**·HCl (67% molar yield). This hydrochloride salt was resuspended in 95% ethanol (500 mL) and refluxed under stirring for 2 h. After cooling to room temperature, the suspension was stirred for 1.5 h and filtered. The filtrate was concentrated to dryness and the residue taken up in acetone (250 mL) and heated at reflux for 2 h. After cooling to room temperature, the suspension was stirred for 1.5 h and filtered. The crystals were washed with acetone (50 mL) and dried under vacuum at 40 °C for 12 h to afford pure **4**·HCl (15 g, 50% molar yield over all). The HPLC retention time and ^{1}H NMR spectrum were identical to those of a reference sample.

(*E*)-*δ*-Chloro-3-[2-(7-chloro-2-quinolinyl)ethenyl-benzenepentanenitrile 5. A suspension of **4**·HCl (20.05 g, 50.2 mmol) in CH_2Cl_2 (900 mL) was stirred under nitrogen at room temperature. Thionyl chloride (7.28 mL, 100.4 mmol) in CH_2Cl_2 (50 mL) was added over 30 min. The reaction mixture was stirred for an additional 30 min with monitoring by HPLC. The brown solution was cooled to 10 °C, and aqueous saturated sodium bicarbonate solution (450 mL) was added over 15 min. The heterogeneous mixture was stirred vigorously for 1 h. After decanting, the organic layer was washed with brine (100 mL), dried ($MgSO_4$, 32 g), filtered, and concentrated to afford **5** as brown oil (17.97 g, 93.8% molar yield). The crude sample containing 15.5% w/w of by-product **11** was used in the next step without further purification. The HPLC retention time and ^{1}H NMR spectrum were identical to those of a reference sample.

7-Cyanomethoxyindole 8. Chloroacetonitrile (6.5 mL, 0.1 mol) was added to crude 7-hydroxyindole **6a** (1.33 g, 0.01 mol) and potassium carbonate (1.38 g, 0.01 mol), and the mixture was vigorously stirred for 24 h at room temperature. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried with anhydrous magnesium sulfate (10 g) and concentrated under reduced pressure to give 1.8 g of black oil. The crude material was purified by filtration on a short path of silica gel (5 g, elution with 100 mL of 1/1 CH_2Cl_2/*n*-hexane) to yield 1.3 g of a white-to-yellow solid which was crystallized from diisopropyl ether (6 mL) at 0 °C for 36 h to give 7-cyanomethoxyindole **8** (1.12 g, 65% molar yield); mp: 76−77 °C. The ^{1}H NMR spectrum was identical to that in the literature.

(*E*)-*δ*-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-7-(cyanomethoxy)-1H-indole-1-pentanenitrile 9. The indole **8** (655 mg, 3.75 mmol) and NaH (60% dispersion in oil; 153 mg, 3.75 mmol) were charged into a dry, 250-mL round-bottom flask. The mixture was maintained at room temperature, and DMSO (33 mL) was carefully added. After stirring for 40 min the solution of the chloride **5** (969 mg, 2.5 mmol) in DMSO (14 mL) was added over 10 min. The reaction was monitored at different times (0, 0.5, 1, 2, 4, 6, 24 h) by HPLC analysis of aliquots. After 24 h, water (50 mL) and acetic acid (0.635 mL) were added with stirring, and the mixture was extracted with CH_2Cl_2 (55 mL). The organic layer was washed with water (3 × 50 mL), dried with $MgSO_4$ (9 g), filtered, and concentrated under vacuum as an oil. The oil was purified by chromatography on silica gel (80 g) using toluene (500 mL), followed by a mixture toluene/ethyl acetate/CH_2Cl_2 90/5/5 (600 mL) as eluent to afford **9** (375 mg, 29% molar yield). The HPLC retention time and ^{1}H NMR spectrum were identical to those of a reference sample.

(*E*)-*δ*-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-7-(cyanomethoxy)-2,3-dihydro-1H-indole-1-pentanenitrile 14. To a solution of crude chloride **6** (15.7 g, approximately 85% purity, 0.03475 mol) in *N*-methylformamide (35 mL) was added 7-cyanomethoxyindoline **13** (10.97 g, 0.063 mol), and the resulting solution was heated at 50 °C under argon for 48 h. Water (50 mL), saturated aqueous sodium bicarbonate (20 mL), and ethyl acetate (70 mL) were added, and after vigorous stirring the organic layer was decanted off. The aqueous layer was extracted with ethyl acetate (2 × 35 mL), and the combined organic layers were washed with diluted sodium bicarbonate (50 mL) and water (50 mL), dried over magnesium sulfate (10 g), filtered, and concentrated under reduced pressure to give 26.35 g of crude material. The crude mixture was purified by filtration on silica gel (800 g, elution with toluene/ethyl acetate/CH_2Cl_2, 8/1/1). The best chromatography fractions (11 g, 0.021 mol) were dissolved in a mixture of ethyl acetate (62 mL) and 2-propanol (248 mL). These were then treated with a solution of oxalic acid monohydrate (2.67 g, 0.021 mol) in 2-propanol (62 mL). After 16 h, the crystals were filtered, washed with 2-propanol (2 × 25 mL), and dried in high vacuum to yield **14**·$C_2H_2O_4$ (10 g, 82% molar yield) as yellow crystals. Calcd For $C_{32}H_{27}ClN_4O$·$C_2H_2O_4$: C, 67.04%; H, 4.80%; N, 9.20%; Found: C, 66.77%; H, 4.75%; N, 9.29%.

5-(3-Bromo-phenyl)-5-hydroxypentanenitrile 16. Preparation of iodo-(3-cyanopropyl)zinc: 2.75 g (42 mM) of zinc dust in 4 mL of anhydrous THF was activated with 0.3 g (1.6 mM) of 1,2-dibromoethane by heating 1 min at reflux under nitrogen. After cooling, 0.16 mL (1.3 mM) of trimethylsilyl chloride was added, and the suspension was stirred for 15 min. A solution of 4-iodobutyronitrile (7.8 g, 40 mM) in 15 mL of anhydrous THF under nitrogen was added over 15 min, and the temperature was maintained at 50 °C overnight.

The iodo-(3-cyanopropyl)zinc reagent (prepared as above) was cooled to below 20 °C. Added to this successively were a solution of **15** (4.25 g, 26.7 mM) in anhydrous THF (40 mL) and of 1 M $TiCl_4/CH_2Cl_2$ (26.7 mL, 26.7 mM) over 15 min (T < 10 °C). After stirring 30 min at 0 °C and 5 h at 20 °C, 38 mL of water and 25 mL of saturated Na_2CO_3 were added. Finally this mixture was diluted with 60 mL of CH_2Cl_2. After 30 min stirring, the salts were separated by filtration and washed with 20 mL of water and 20 mL of CH_2Cl_2. The organic layers were washed with 20 mL of brine, dried with $MgSO_4$, filtered, and evaporated to give 7 g of of crude oil. Purification by chromatography on silica gel (hexane 70/EtOAc 30) and evaporation of the fractions yielded pure **16** (5.08 g, 75% molar yield).

5-(3-Bromo-phenyl)-5-chloropentanenitrile 17. A solution of **16** (2.05 g, 8.06 mmol) in CH_2Cl_2 (130 mL) was stirred under nitrogen at 0 °C. Thionyl chloride (1.17 mL, 100.4 mmol) in CH_2Cl_2 (10 mL) was added over 10 min. The reaction mixture was stirred for a further 30 min (monitoring by HPLC). The resulting brown solution was cooled to 10 °C, and an aqueous saturated $NaHCO_3$ solution (50 mL) was added dropwise over 15 min. The mixture was stirred vigorously for 30 min. After decanting, the organic layer was washed with brine (40 mL), dried ($MgSO_4$, 9 g), filtered, and concentrated to a brown oil (2 g, 90% molar yield). The crude mixture was used in the next step without further purification.

5-(3-Bromo-phenyl)-5-(7-cyanomethoxy-2,3-dihydro-1H-indole)pentanenitrile 18. *(a) Via S_N2 Displacement of Chloride **17.*** To a solution of crude chloride **17** (755 mg, 85% purity, 2.34 mmol), in 5 mL of *N*-methylformamide (NMF) was added 7-cyanomethoxyindoline **13** (817 mg, 4.7 mmol). The reaction mixture was heated to 50 °C under argon for 28 h. Water (5 mL), saturated aqueous sodium carbonate (5 mL), and ethyl acetate (15 mL) were added, and after vigorous stirring the organic layer was decanted off. The aqueous layer was extracted with ethyl acetate (15 mL), and the combined organic layers were washed with sodium carbonate (15 mL) and water (15 mL), dried over magnesium sulfate (8 g), and concentrated under reduced pressure to give 1.72 g of crude material. The oil was purified by chromatography on silica gel (120 g) using a mixture ethyl acetate/cyclohexane (25/75) as eluent to afford **18** (590 mg, 72% molar yield).

*(b) Via the Katritzky Adduct **20.*** 7-Cyanomethoxyindoline **13** (2.26 g, 0.01 mol) was added to a solution of benzotriazole (1.2 g, 0.01 mol) in diethyl ether (40 mL) under argon. After 5 min, 0.4 nm molecular sieves (3 g) and 3-bromobenzaldehyde **15** (1.906 g, 0.01 mol) in diethyl ether (10 mL) were added, and the yellow solution was stirred at room temperature for 20 h under argon to afford the adduct **20**. Iodo-(3-cyanopropyl)zinc in THF prepared as above (15 mL, approximately 0.0075 mol) was then added to the crude adduct **20** (ether solution, 12.5 mL, approximately 0.0025 mol) under argon, and the heterogeneous mixture was stirred for 2 h. Water (25 mL) and ethyl acetate (25 mL) were added, the solid was filtered and discarded, the organic layer was decanted, and the aqueous layer was extracted twice with ethyl acetate (25 mL). The combined organic layers were dried on magnesium sulfate and concentrated under reduced pressure. The resulting solid was purified by chromatography (200 g silica gel, elution with toluene/CH_2Cl_2/ethyl acetate, 90/5/5) to yield **18** (0.7 g, 68% molar yield).

Alternative via Grignard Reagent. To the crude adduct **20** prepared above (45 mL of solution, 0.009 mol) was added the Grignard reagent prepared from 2-(3-chloropropyl)-1,3-dioxolane (5.3 g, 0.035 mol), magnesium (2.4 g, 0.099 mol), 1,2-dibromoethane (0.7 g, 0.0037 mol), and iodine (a small crystal) in THF (26 mL). After 1 h, the reaction mixture was quenched with saturated ammonium chloride (100 mL), diluted with water (100 mL), and extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by silica gel filtration (200 g, elution with cyclohexane/ethyl acetate 8/2) to yield 3.8 g (104% molar yield) of a yellow oil containing approximately 20 wt % of starting material (NMR estimation). The crude oil was dissolved in absolute ethanol (25 mL). *p*-Toluenesulfonic acid monohydrate (1.2 g, 0.0063 mol) and hydroxylamine hydrochloride (0.565 g, 0.008 mol) were added, and the mixture was heated under reflux for 2.5 h. After cooling, addition of saturated aqueous sodium bicarbonate (30 mL) and evaporation of ethanol under reduced pressure, the mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over magnesium sulfate (10 g) and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (elution with toluene/ethyl acetate/CH_2Cl_2 9/1/1) to yield **18** as a yellow oil (2.28 g, 62% molar yield overall).

5-(3-Bromo-phenyl)-5-(7-cyanomethoxy-1H-indole)-pentanenitrile 19. To a solution of **18** (0.3 g, 0.7 mmol) in 3 mL of anhydrous THF was added dropwise a solution of DDQ (181 mg, 0.8 mmol) in 4 mL of THF over 5 min. The black mixture was evaporated to dryness, the residue taken up in 10 mL of CH_2Cl_2 and washed twice with 2 mL of 1 N aqueous sodium hydroxide. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over magnesisum sulfate, and evaporated to dryness to afford 0.33 g of a red oil (116% molar yield). The crude mixture was purified by flash chromatography on silica gel (10 g) eluting with *n*-hexane/ethyl acetate (7/3) to afford **19** (0.24 g, 80% molar yield).

1-(3-Bromophenyl)-4-cyano-butanone 21. A 50-mL flask was charged with DMSO (1.4 mL, 20 mmol) and 10 mL of CH_2Cl_2. After cooling to −50 °C a solution of trifluoroacetic acid (1.15 mL, 15 mmol) in 5 mL of CH_2Cl_2 was added over 10 min. After 10 min, a solution of **14** (2.54 g, 10 mmol) in 6 mL of CH_2Cl_2 was added dropwise, and the reaction mixture was stirred for 30 min at −50 °C. The reaction was treated with triethylamine (4 mL, 28.7 mmol), and the temperature was allowed to rise to 20 °C over 1 h. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (10 mL). The organic layer was dried over magnesium sulfate and evaporated to dryness to afford 2.8 g of crude oil (112% molar yield). Purification on silica gel (100 g) eluting with CH_2Cl_2 afforded **21** (1.57 g, 63% molar yield) as a slightly yellow oil.

(+)-5-(3-Bromo-phenyl)-5-hydroxypentanenitrile 22a. *(a) Via (S)-Oxazaborolidine/Borane Reduction.*[18] A 100-mL flask was charged with the (*S*)-oxazaborolidine catalyst **26** (554 mg, 2 mmol), 10 mL of anhydrous toluene, and *N*,*N*-diethylaniline borane (4 mL, 22.4 mmol). To this mixture was added dropwise over 1.5 h a solution of **21** (5.04 g, 20 mmol) in 40 mL of anhydrous toluene. After 1 h at room temperature, the reaction was quenched by successive addition of methanol (10 mL) and 1 N aqueous HCl (15 mL). After 20 min, the organic layer was decanted, and the aqueous layer was extracted with toluene (2 × 15 mL). The combined organic layers were washed with 15 mL of 1 N

HCl and then 10 mL of water, dried over magnesium sulfate, and evaporated to dryness to afford **22a** (4.75 g, 93% molar yield) as a yellow oil; $[\alpha]^{20}_D = +18.3°$ ($c = 1$, MeOH). A 76% de [88/12] was determined by ^{1}H NMR on the Mosher's esters prepared with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid.[20]

(b) Via Ru-Catalyzed Asymmetric Transfer Hydrogenation.[19] A 10-mL flask was charged with **21** (504 mg, 2 mmol), the (*S*,*S*)-Noyori-catalyst **27** (10 mg, 15.7 μmol), and 1 mL of a 5:2 mixture of formic acid/triethylamine. The reaction mixture was stirred at 28 °C for 24 h, diluted with 10 mL of water, and extracted with 10 mL of toluene. The organic layer was washed with 5 mL of 1 N HCl and twice with water (10 mL). The organic layer was dried on magnesium sulfate and evaporated to dryness to afford **22a** (0.48 g, 95% molar yield) as a yellow oil. An 84% de [8/92] was determined by ^{1}H NMR on the Mosher's esters.

(−)-5-(3-Bromo-phenyl)-5-chloropentanenitrile 23. A 250-mL flask was charged with *N*-chlorosuccinimide (2.32 g, 17.4 mmol) and 70 mL of CH_2Cl_2. A solution of triphenylphosphine (4.6 g, 17.5 mmol) in 24 mL of CH_2Cl_2 was added dropwise over 10 min at 5 °C. A solution of **22a** (4 g, 15.7 mmol, 76% e.e.) in 55 mL of CH_2Cl_2 was added, and the resulting mixture was stirred at room temperature for 18 h. The reaction was evaporated to dryness, and the residue was percolated on silica gel using an 8:2 cyclohexane/ethyl acetate mixture to afford **23** (2.61 g, 61% molar yield) as an oil; $[\alpha]^{20}_D = -50.3°$ ($c = 1$, MeOH).

(+)-5-(3-Bromo-phenyl)-5-(7-cyanomethoxy-2,3-dihydro-indol-1-yl)pentanenitrile 24. To a solution of **23** (2.5 g, 9.17 mmol), in 12.5 mL of *N*-methylformamide (NMF) was added 7-cyanomethoxyindoline **13** (3 g, 18.3 mmol). The reaction mixture was heated at 50 °C under argon for 46 h. Water (16 mL), saturated aqueous sodium carbonate (16 mL), and ethyl acetate (30 mL) were added, and after vigorous stirring the organic layer was decanted off. The aqueous layer was extracted with ethyl acetate (30 mL), and the combined organic layers were washed with sodium carbonate (40 mL), dried over magnesium sulfate (8 g), and concentrated under reduced pressure to give 10 g of crude material. The crude oil was purified by chromatography on silica gel (120 g) using a mixture of ethyl acetate/cyclohexane (2/8) as eluent to afford **24** (2.53 g, 67% molar yield) as an oil; $[\alpha]^{20}_D = +133.9°$ ($c = 1$, MeOH), Chiral LC: 84/16 (68% ee).

(+)-5-(3-Bromo-phenyl)-5-(7-cyanomethoxy-indol-1-yl)-pentanenitrile 25: obtained via the DDQ oxidation of **24** as above; $[\alpha]^{20}_D = +95°$ ($c = 1$, MeOH) and +106.8° ($c = 0.6$, $CHCl_3$), chiral LC: 83.6/16.4 (67.2% ee).

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