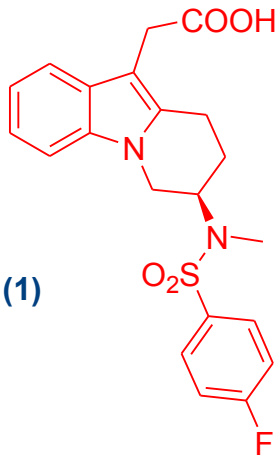
CRTH2 Antagonist MK-7246: A Synthetic Evolution from Discovery through Development

Carmela Molinaro*, Paul G. Bulger*, Ernest E. Lee, Birgit Kosjek, Stephen Lau, Danny Gauvreau, Melissa E. Howard, Debra J. Wallace, and Paul D. O'Shea



MK-7246 (1)

J. Org. Chem. **2012**, 77, 2299−2309

Feng Zhang

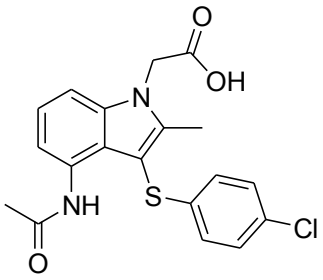
Current Literature

05.12.2012

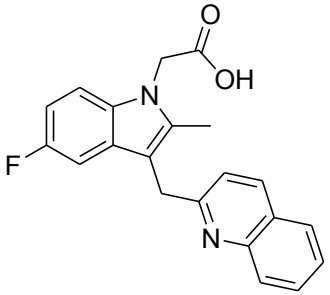
Introduction and Background:

- CRTH2 (DP2) is one of the two high-affinity transmembrane receptors for prostaglandin d2 (PGD2).
- PGD2 has been implicated as a mediator of allergic inflammation and diseases including asthma, allergic rhinitis, and atopic dermatitis.
- The first PGD2 receptor characterized, DP, is known mainly for its role vasodilatation.
- By contrast the more recently identified CRTH2 has been found to play a role in leukocyte activation.
- Biological and genetic data suggest that the downstream events triggered by activation of CRTH2 through binding to PGD2 play a key role in stimulating latephase allergic inflammation.
- The hypothesis that blockade of the CRTH2 receptor could provide a novel mechanism for treatment of chronic allergic disease.
- Many companies have engaged in CRTH2 antagonist programs which have reached various stages of preclinical and clinical development.

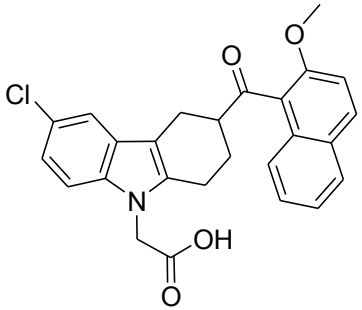
Some of DP_2 receptor antagonists in development



AZD-1981
Phase II



OC-459
Phase II



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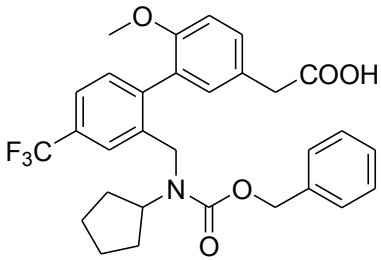
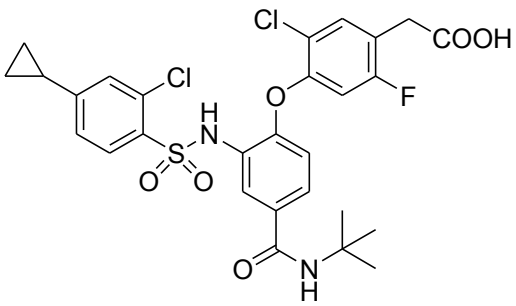
Phase II



AM-211
Phase I



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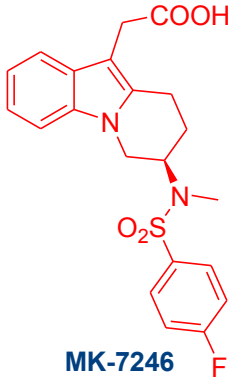
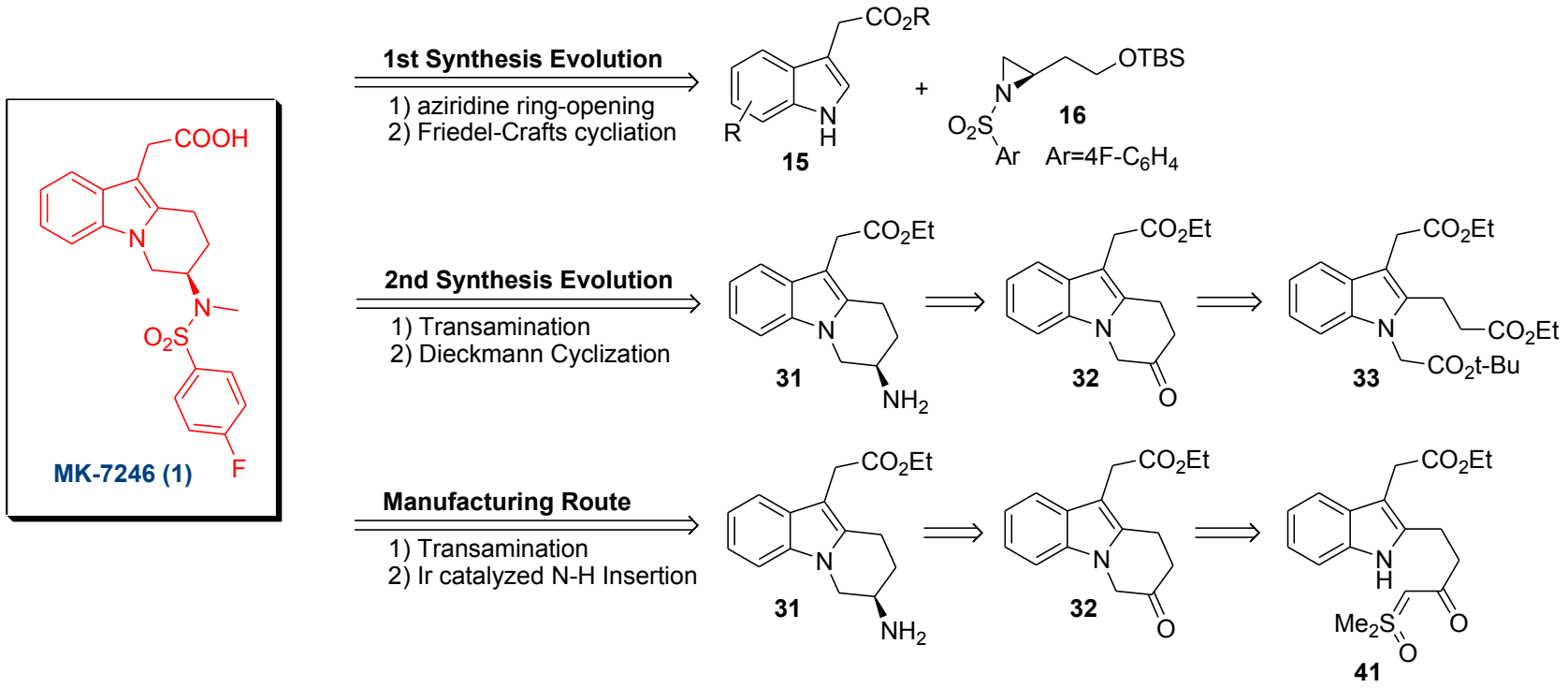
Phase II



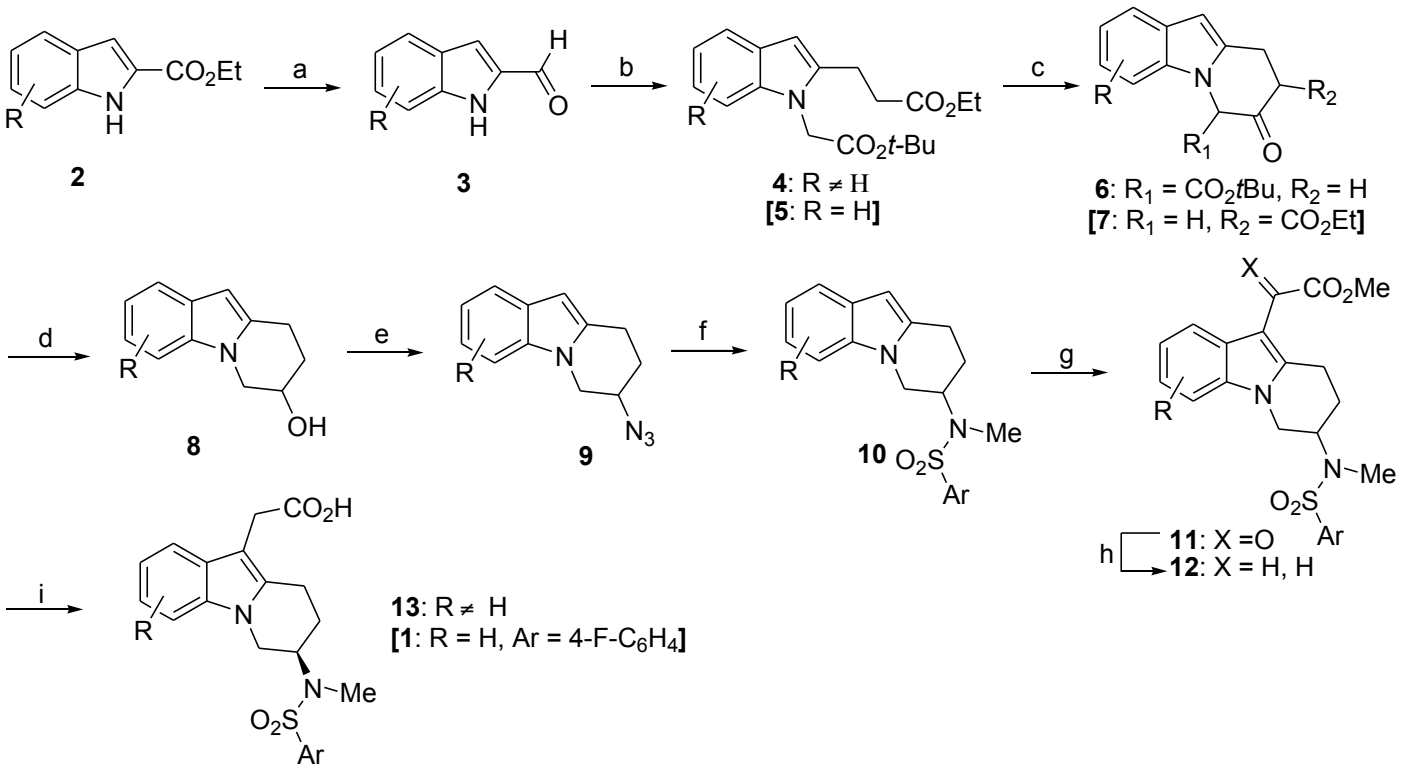
MK-7246

Norman, P. Expert Opin. Invest. Drugs **2010**, 19, 947–961.

Abstract


COOH
N
N
O2S
F
MK-7246 (1)
1st Synthesis Evolution
1) aziridine ring-opening
2) Friedel-Crafts cycliation
CO2R
R
N
H
15
+
OTBS
N
O2S
Ar
16
Ar=4F-C6H4
2nd Synthesis Evolution
1) Transamination
2) Dieckmann Cyclization
CO2Et
N
31
NH2
CO2Et
N
32
O
CO2Et
N
CO2Et
CO2t-Bu
33
Manufacturing Route
1) Transamination
2) Ir catalyzed N-H Insertion
CO2Et
N
31
NH2
CO2Et
N
32
O
CO2Et
N
H
Me2S
O
O
41

Original Synthesis of MK-7246 (1) and Analogues (13)

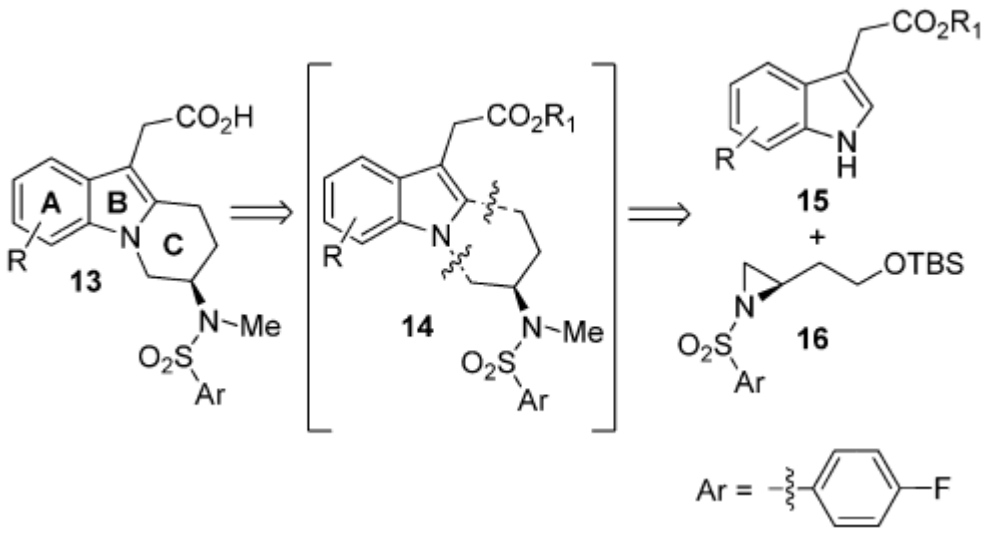


Reagents: (a) 1. $LiAlH_4$; 2. MnO_2; (b) 1. Ph_3PCHCO_2Et; 2. $BrCH_2CO_2t$-Bu, Cs_2CO_3; 3. H_2, Pd/C; (c) KO*t*-Bu; (d) 1. silica gel, toluene, reflux; 2. $NaBH_4$; (e) 1. MsCl, Et_3N; 2. NaN_3; (f) 1. H_2, Pd/C; 2. $ArSO_2Cl$, Et_3N; 3. NaH, MeI; (g) 1. $(COCl)_2$; 2. MeOH; (h) 1. $NaBH_4$; 2. Et_3SiH, TFA; (i) 1. chiral HPLC; 2. LiOH, THF

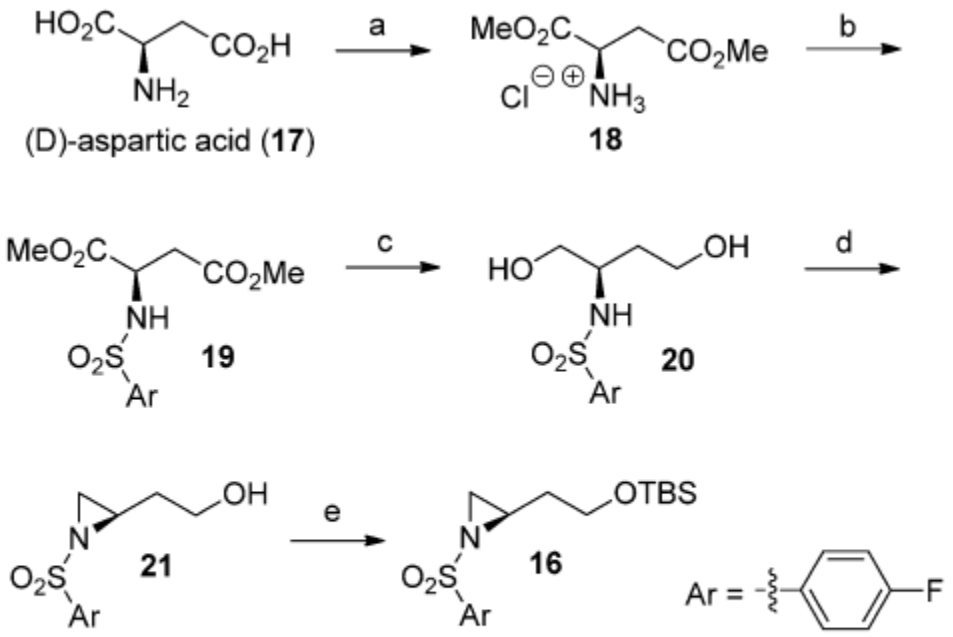
Drawbacks

- the synthesis was linear with the indole core being incorporated in the first step, limiting the possibilities for subsequent diversification.
- synthetic routes suffered from tedious separation and lower overall yield. (at 18 steps, ~10% overall yield, including a late-stage chiral separation)
- long time, the synthesis time per analogue was about 3–4 weeks.

Retrosynthetic Analysis: Aziridine Ring-Opening Reaction as the Key Coupling Strategy

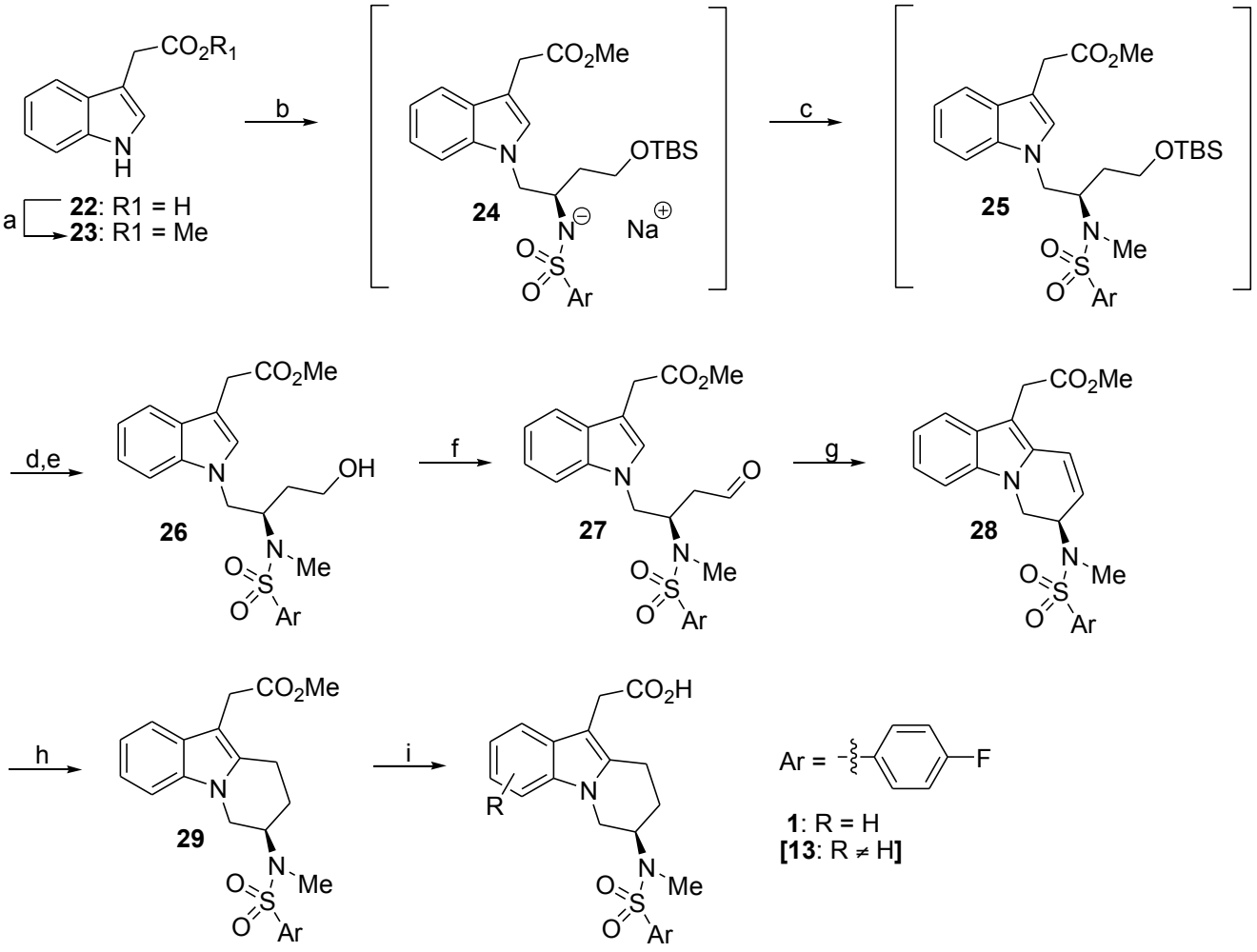


Preparation of Aziridine 16



Reagents: (a) $SOCl_2$, MeOH, 99%; (b) $ArSO_2Cl$, Et_3N, THF, 93%; (c) $NaBH_4$ (5 eq), EtOH, 60%; (d) ADDP, *n*-Bu_3P, THF, 77%; (e) TBSCl, Et_3N, THF, 84%.

Synthesis of MK-7246 (1) Using the Aziridine Ring-Opening Strategy



Reagents: (a) MeOH, cat H_2SO_4, 81%; (b) 1. KHMDS, DMF; 2. **16**; (c) MeI; (d) HCl, 63% (69 LCAP) from **16**; (e) reslurry in EtOAc/MTBE/*n*-heptane, 96% (83 LCAP); (f) $(COCl_2)_2$, DMSO, Et_3N, CH_2Cl_2; PPTS, toluene, 60 °C, 80% from **26**; (h) H_2, Pd/C, EtOAc, 91%; (i) LiOH, THF, 97%.

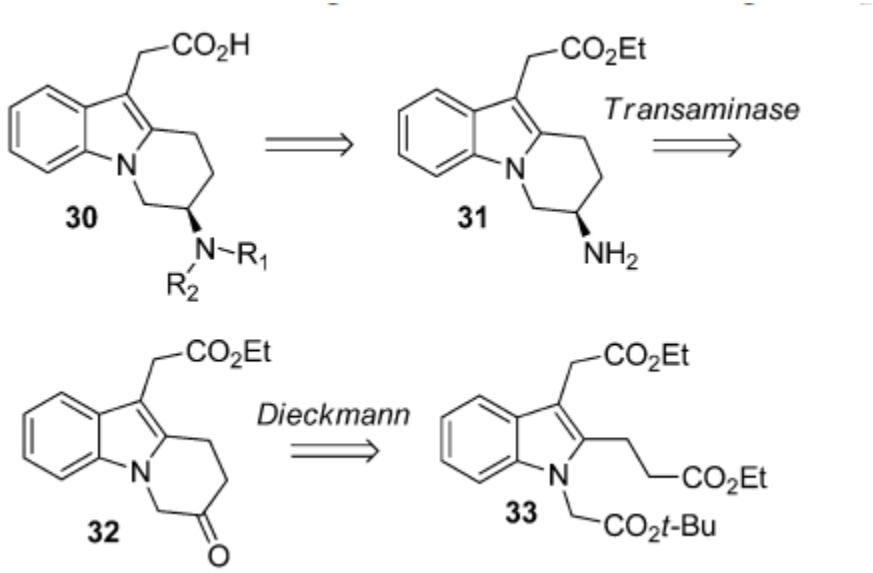
Advantages

- set the stereocenter on the molecules eliminating chiral separations
- overall 11 steps, 15% yield from D-aspartic acid
- less than 1 week processing time on laboratory scale
- with the potential for structural diversification at many sites
- scalable to the extent that 1−10 kg quantities of MK-7246 (1) could be prepared, enough to supply the early phase I clinical trials and animal toxicity studies

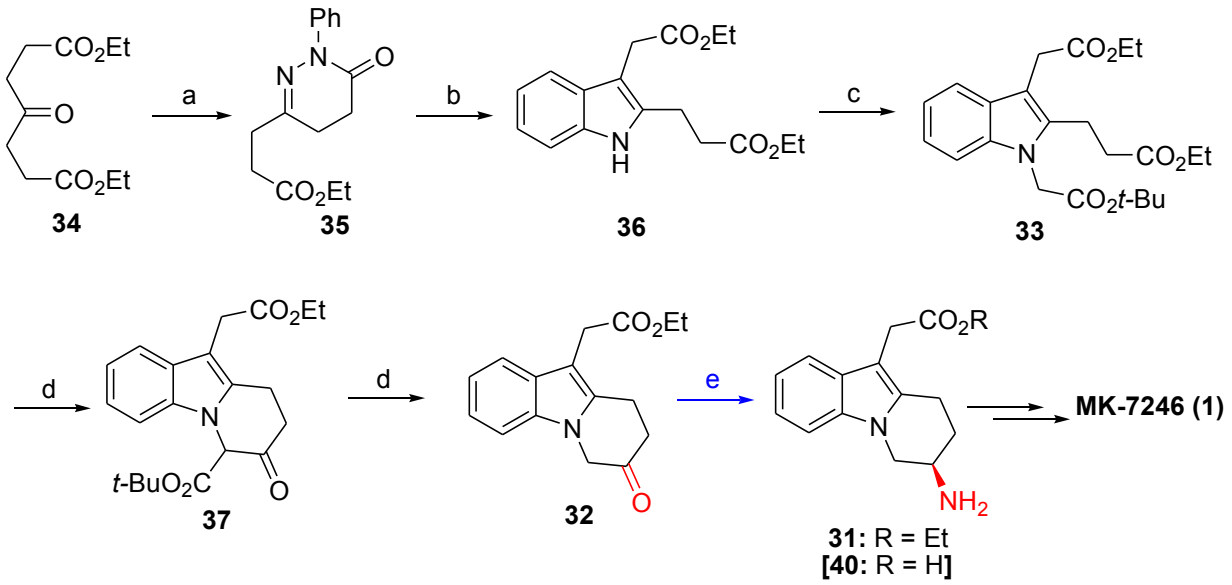
Drawbacks

- moderate yields, processing difficulties for several steps, and instability of certain intermediates combined to render this route impractical for the production of the significantly larger quantities (>10 kg) of MK-7246 (1) needed for late-stage development into phase II and beyond.

Retrosynthetic Analysis: An Enzymatic Reaction Installs the Amine-Bearing Stereocenter in a Single Step



Preparation of Transaminase Ketone Precursor 32: Dieckmann Cyclization Route



Reagents: (a) $PhNHNH_2 \cdot HCl$, toluene, reflux, 87%; (b) H_2SO_4, EtOH, reflux, 75%; (c) $BrCH_2CO_2t$-Bu, Cs_2CO_3, DMF, 93%; (d) KO*t*-Bu, THF, 64%; (e) silica gel, toluene, reflux, 88%; (e) CDX -017 (4.3 wt%), PLP, *i*-$PrNH_2$, PH 8.5 Et_3N buffer, aq DMSO, 45 °C, 80 - 81% assay yield of 31, 98 -99% ee.

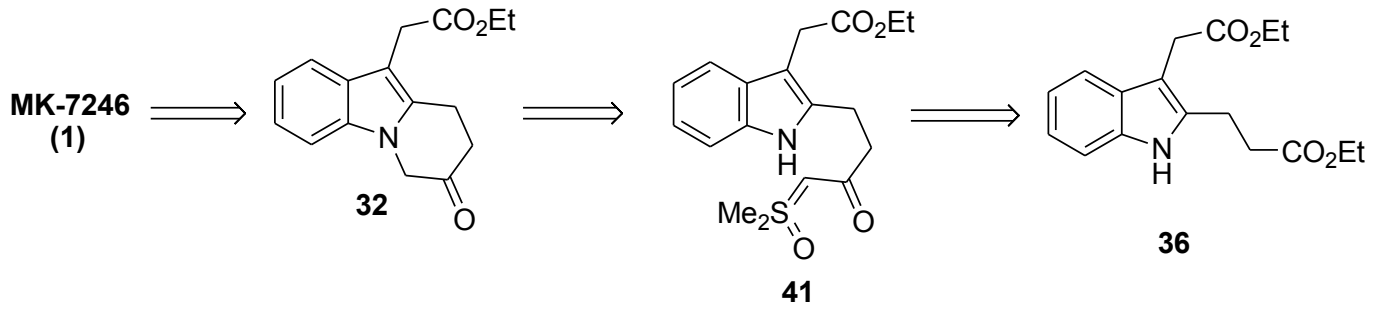
Advantages

- This amine was highly valuable for our Medicinal Chemistry colleagues since it allowed subsequent SAR of positions R1 and R2 of compound **30** in only two steps.

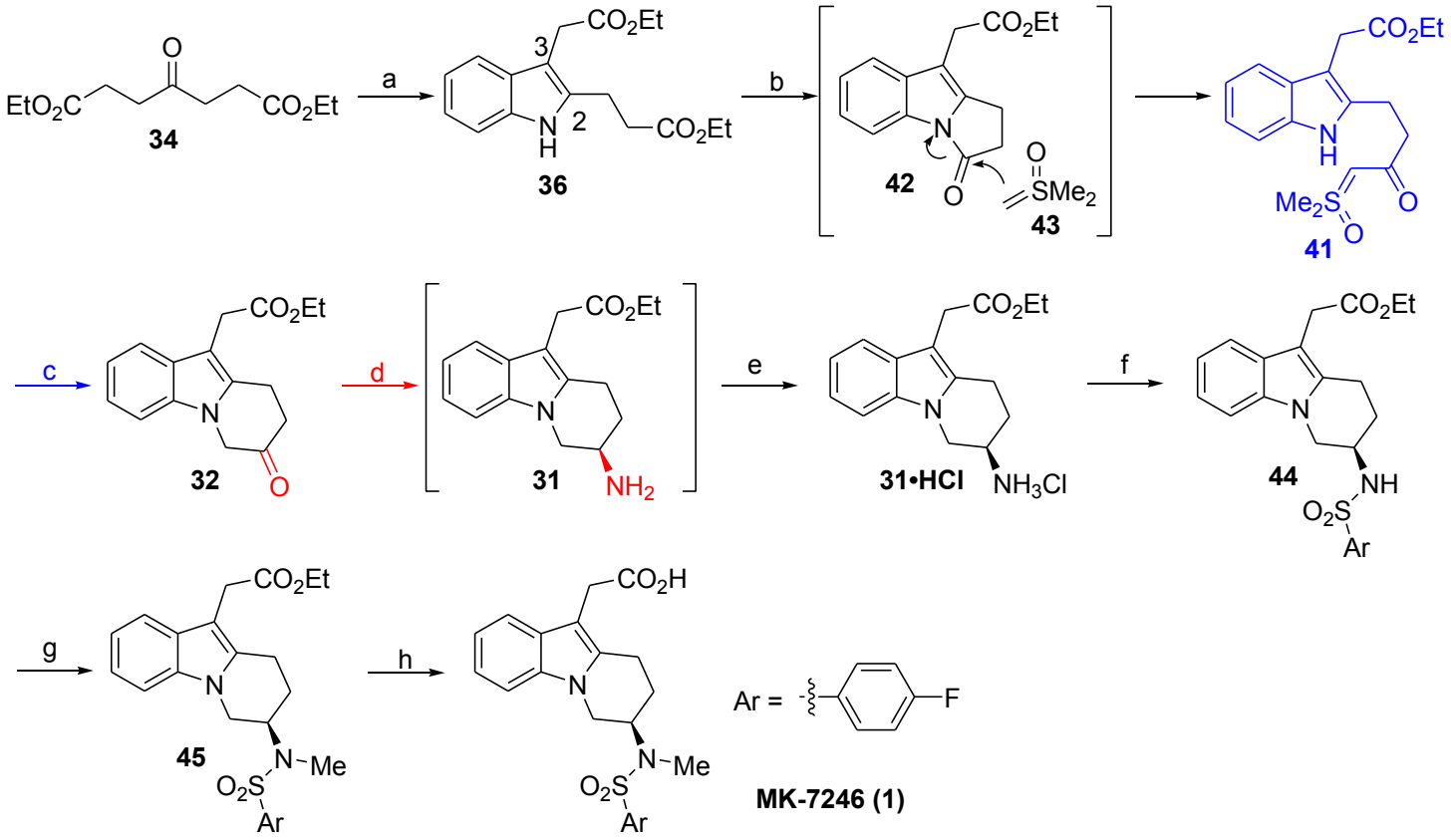
Drawbacks

- the relatively high number of steps
- the paucity of crystalline intermediates and need for chromatographic purification after each step
- the lack of regioselectivity in the cyclization reaction.

Revised Retrosynthetic Analysis: N–H Carbenoid Insertion Approach to Tricyclic Ketone 32



Manufacturing Route to MK-7246 (1)



Reagents: (a) $PhNHNH_2$•HCl, $ZnCL_2$, toluene, 105°C; (b) Me_3SOI, KO*t*-Bu, THF, 77% from **34**; (c) $[IrCl(COD)]_2$ (1 mol%), toluene/DMF, 85°C, 83%; (d) CDX -017 (4.3 wt%), PLP, *i*-$PrNH_2$, PH 8.5 Et_3N buffer, aq DMSO, 45°C, 81% AY, 98 -99% ee; (e) HCl, IPA/CPME, 76% from **32**; (f) $ArSO_2Cl$, aq Na_2CO_3, IPAc, 89%; (g) MeI, K_2CO_3, DMF, 96%; (h) aq LiOH, THF/EtOH, 99%.

Conclusion

- the route proceeded in eight steps and 49% overall yield from commercially available starting materials
- required no chromatographic purifications
- amenable to pilot-plant scale production (>100 kg)

Highlights

- an Ir-catalyzed intramolecular N−H insertion of sulfoxonium ylide **41**
- conversion of ketone **32** to amine **31** in a single step with excellent enantioselectivity through a transaminase process
- Reactions such as these illustrate the enabling impact and efficiency gains that innovative developments in chemo- and biocatalysis can have on the synthesis of pharmaceutically relevant target molecules