



Trip Report for
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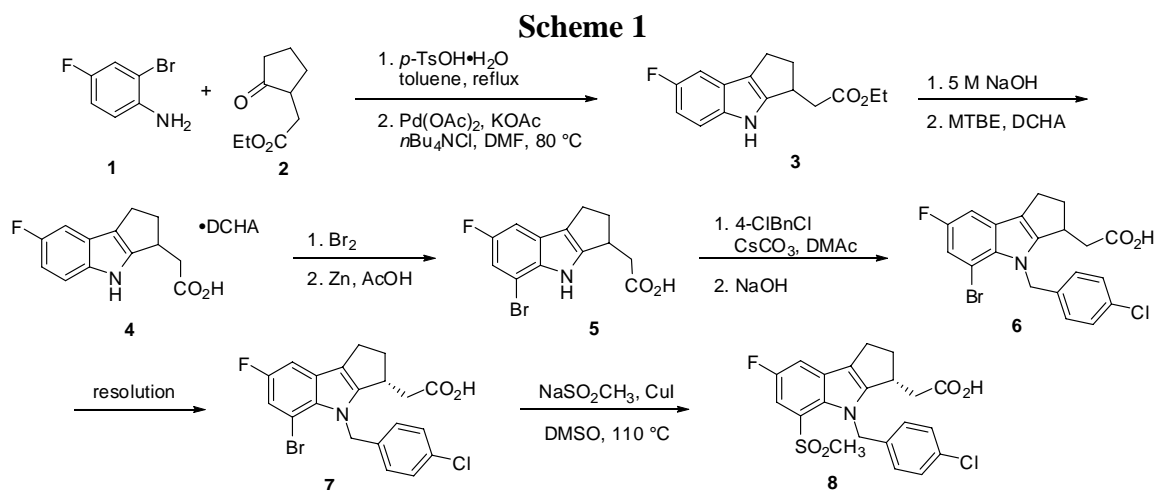
***Abstract:** The 40th annual ACS Mid-Atlantic Regional Meeting (MARM) was organized around the theme “Chemistry and Health”. The program included two poster sessions and over sixty presentations on topics such as Analysis of Biomolecules and Green Chemistry. The keynote lectures were given by Ronald Breslow and Roald Hoffmann.*

“An Efficient Asymmetric Synthesis of Tricyclic Indole Prostaglandin D2 Receptor Antagonist Laropiprant”

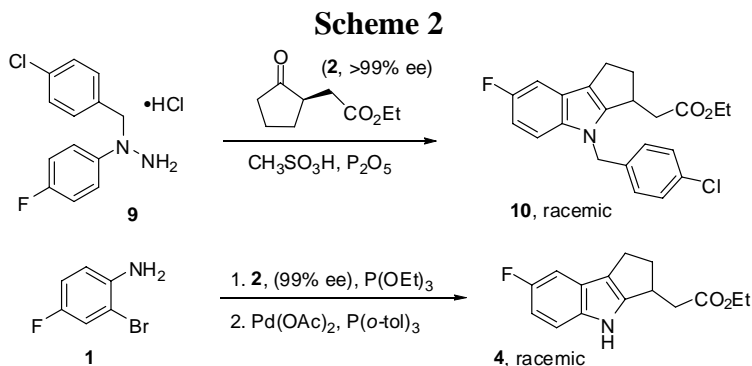
Peter Maligres, Merck and Co., Inc.

Laropiprant (**5**, Scheme 1) is a compound developed by Merck for the treatment of allergic rhinitis. Dr. Maligres of Merck described the evolution of the development of laropiprant through several generations. Key improvements were the innovation of asymmetric hydrogenation conditions and the use of a regioselective condensation reaction with an aryl hydrazine.

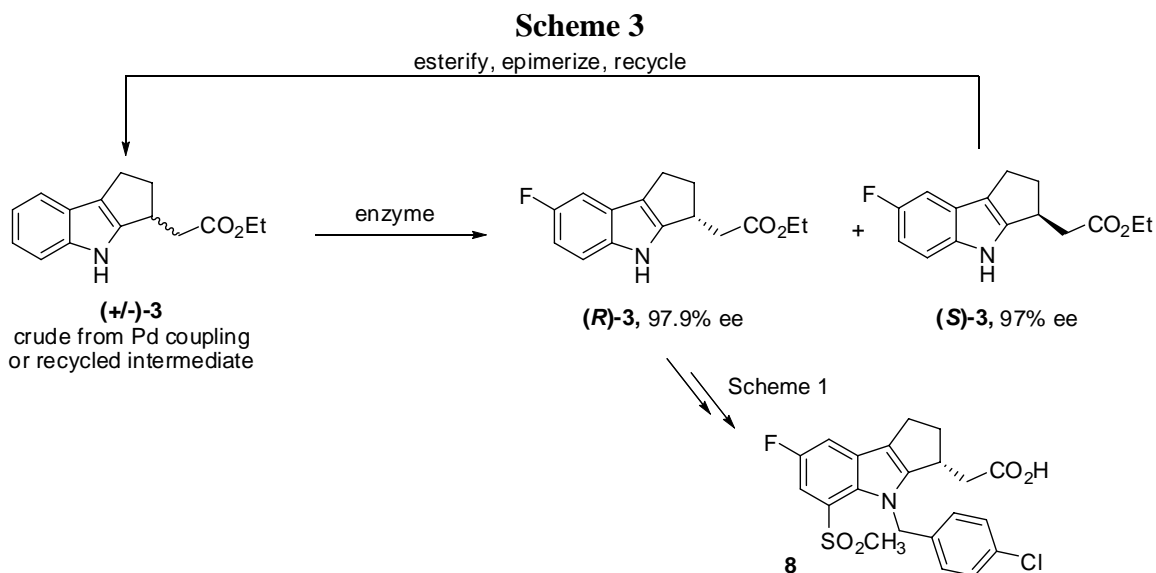
The first-generation synthesis (Scheme 1) proceeded in six steps with 10% overall yield. The route was racemic until resolution at a late stage, and made use of undesirable reagents such as bromine, zinc, the expensive base CsCO₃ and copper iodide.



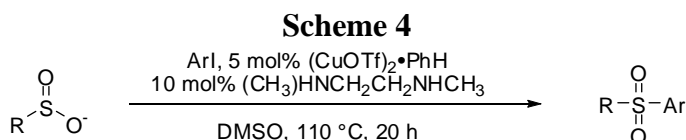
In order to make the route suitable for industrial scale-up, it was important to avoid a traditional chiral resolution at the end of the synthesis, which sacrifices half the material. Establishing the stereogenic center early in the route would be very beneficial. In previous work (Scheme 2) it had been discovered that the enantiopure cyclopentane acetate **2** undergoes complete racemization upon Fischer-indole cyclization with hydrazine **9**. In the same way, condensation of **2** with an aniline followed by intramolecular Heck reaction yielded purely racemic indole **4**.



The group therefore considered resolution of the next intermediate, the indole ester **3**. After screening for an appropriate biocatalyst, the lipase from *Pseudomonas fluorescens* was selected for optimization and development (Scheme 3). The group was able to obtain greater than 97% ee after 45 h of aging, and in tests done to determine the enzyme's recycling potential. They found that the recovered enzyme did not show any loss of catalytic potential after going through at least three catalytic cycles of use.

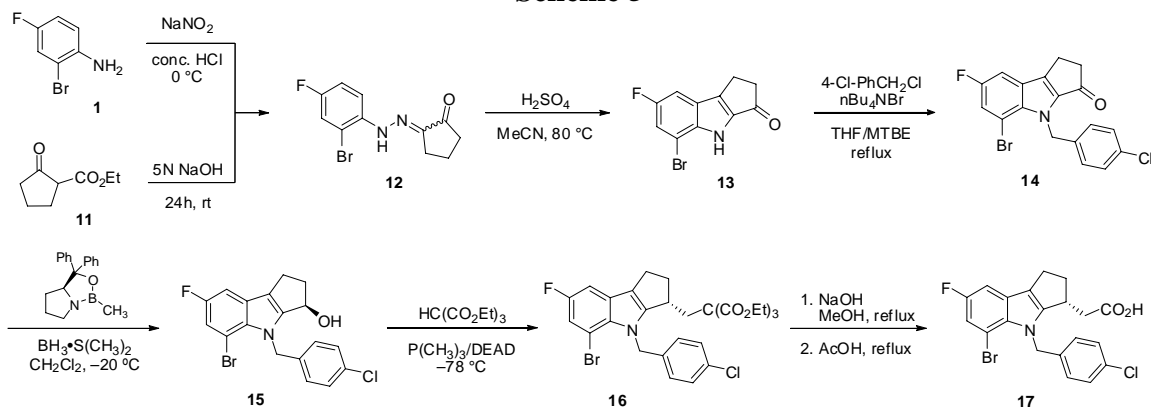


Having demonstrated the feasibility of the modified route, Merck developed a kilogram-scale process for the preparation the desired enantiomer of ester **3**. However, the overall synthesis of laropiprant remained reliant on problematic reagents. At the sulfonylation step, the team was able to reduce the copper iodide loading from greater than 50 mol% to 5 mol% by switching the substrate to an aryl iodide versus an aryl bromide (Scheme 4), although this improvement did not go far enough to green the process.



The Merck team returned to the Fischer-indole synthesis, this time rethinking the way the functional motifs were distributed to the substrates (Scheme 5), and setting the stereocenter through asymmetric reduction followed by Mitsunobu inversion.

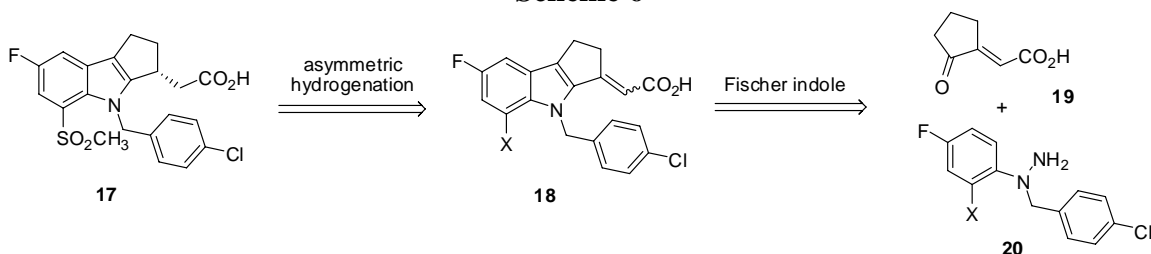
Scheme 5



The synthesis of the keto-hydrazone **12** by Japp-Klingemann condensation had several advantages for an industrial-scale process: use of the commercially available bromoaniline **1** removes the need for a bromination step later in the synthesis, and zinc and bromine are removed from the process; the keto-hydrazone **12** crystallizes *in situ* and can be isolated from the reaction mixture by filtration as a free-flowing solid in 95% yield; benzylation of the indoline rather than the free hydrazine (resulting in hydrazine **9**, as in Scheme 2) avoids complications stemming from nitrogen gas evolution or over-alkylation.

Finally, Dr. Maligres presented a variation of the synthesis whereby the stereogenic center is installed by a new asymmetric hydrogenation (Scheme 6).

Scheme 6



Hydrogenation presents special challenges for industrial work. The catalyst and ligands can be expensive or unavailable at large scale, they are air-sensitive and there is hydrogen gas. However, catalytic hydrogenation is perhaps the most atom-efficient method for reduction, and Merck is trying to develop it as a tool that will lead to more efficient, economic and environmentally beneficial large-scale syntheses.

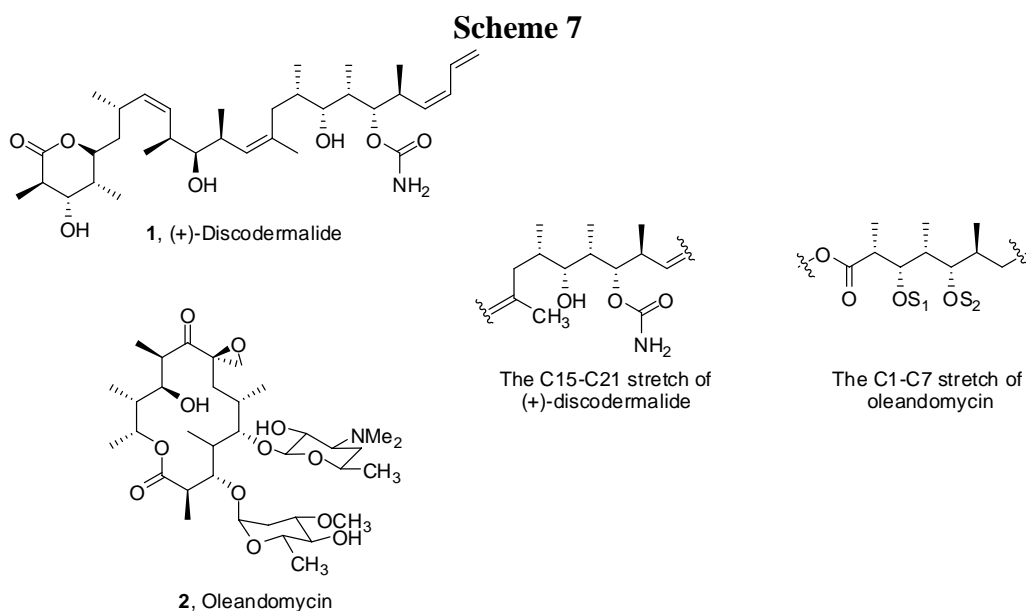
After catalyst screening and preliminary optimization, the conditions for hydrogenation had to be adapted to large scale. At useful and industrial-scale concentrations ($>0.2\text{ M}$), solubility of the *E*-precursor **18** was a serious problem. The reaction mixtures were thick slurries and hydrogenations were slow and not reproducible. The group screened close to 30 different salts for solubility under the reaction conditions. Trimethylguanidine (TMG) was chosen, but even with improved solubility, catalyst loadings $> 0.8\text{ mol } \%$ were needed to achieve 95% conversion. However, when the TMG salt was prepared by

crystallization prior to use rather than *in situ*, catalyst loadings as low as 0.3 mol % gave complete conversion. The assumption was that the crystallization step effectively rejects catalyst poisons produced during the synthesis of **18**. Under optimized conditions (S-BINAP, ruthenium catalyst with 10 psi of hydrogen at 50 °C), the group achieved complete conversion and 91% ee. Higher pressures and temperatures eroded the optical purity of the product, and the group did some interesting and thorough work to elucidate the mechanism and intermediates at play. For further reading, see: *J. Am. Chem. Soc.* **2006**, *128*, 17063–17073; *J. Org. Chem.* **2005**, *70*, 8385–8394; *Org. Lett.* **2002**, *4*, 4423–4425; *J. Org. Chem.* **2005**, *70*, 268–274; *Tetrahedron: Asymm.* **2005**, *16*, 3094–3098; *J. Med. Chem.* **2007**, *50*, 794–806.

“Strategies and Methods for the Synthesis of Natural Products”

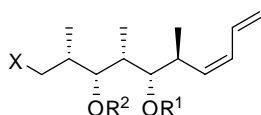
Kathlyn A. Parker, Stony Brook University, Stony Brook, New York

Dr. Parker presented some work her group has performed toward the synthesis of discodermalide to illustrate a new synthetic strategy she termed deconstruction-reconstruction. (+)-Discodermalide is a natural product found in some sea sponges, and has become of great interest in connection with antitumor treatments (Scheme 7).



Parker’s group recognized the same stereopentad in oleandomycin as in discodermalide, and as oleandomycin is a cheaply available fermentation product, they imagined chopping up oleandomycin and elaborating the resulting freed stereopentad fragment into one of the C14–C24 iodides **3b–3d** (Scheme 8), each of which had been used as a key intermediate in a total synthesis of the natural product.

Scheme 8



- 3a** X = I, R¹ = TBS, R² = PMB
3b X = I, R¹ = TES, R² = PMB
3c X = I, R¹ = PMB, R² = TBS
3d X = I, R¹ = TES, R² = TBS
3e X = OH, R¹ = TES, R² = TBS

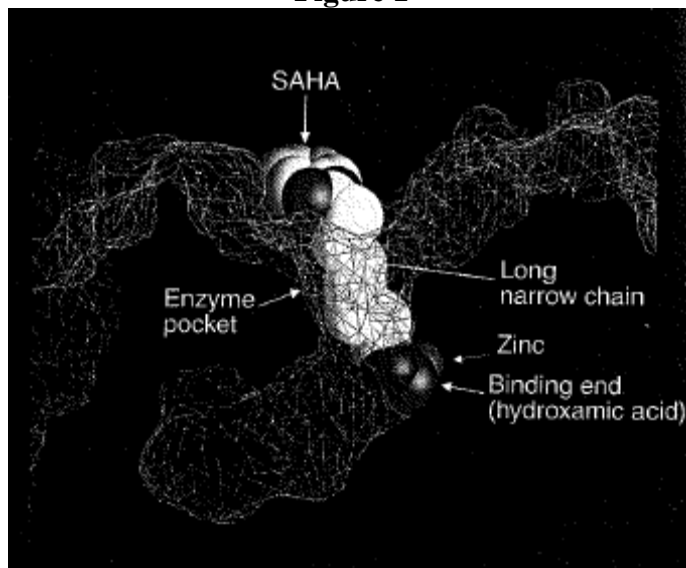
The preparation of alcohol **3e** was effected in twelve steps and ~ 7% overall yield. This demonstrated proof-of-principle for the conversion of mass-produced macromolecules to value-added synthetic building blocks. For further reading, see: *Org. Lett.* **2007**, *9*, 4793; *Org. Lett.* **2008**, *10*, 1353; *Org. Lett.* **2005**, *7*, 1825.

Plenary lecture: “SAHA (Vorinostat), an FDA Approved Anticancer Compound with a Novel Mechanism of Action”

Ronald Breslow, Columbia University, New York, New York

This presentation described the development of the histone deacetylase inhibitor (**Fig. 1**) suberoylanilide hydroxamic acid [SAHA; vorinostat (Zolinza), Figure 1], an FDA approved anticancer compound with a novel mechanism of action. This compound causes growth arrest in a variety of transformed cells through acetylation of various protein targets at concentrations that are not toxic to normal cells.

Figure 1



Through studies of erythroleukemia cells it was found that DMSO, initially used as a solvent, turned two-thirds of the cells into hemoglobin. This finding initiated the search for other small molecules. The first study found that polar, small-molecule solvents had the same effect. Amides were found to be more potent than DMSO. The first compound the Breslow group synthesized, hexamethylene bisacetamide (HMBA, Figure 2), linked two amide groups to take advantage of the chelate effect. This compound had 5 mM potency and had the optimum polymethylene chain length of six methylenes. As

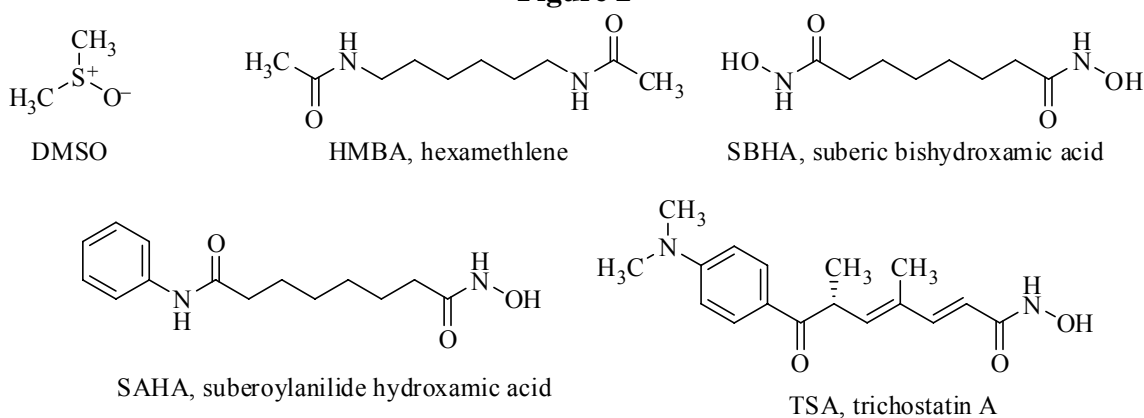
methylene groups were added or deleted the potency dramatically decreased. Through *in vitro* testing this compound was approved for clinical studies, however it was found not to be potent enough and so therefore more research was needed.

It was then realized through SAR studies that there was binding of solvent to a target, not other physical interactions going on. This meant that the receptor must have a metal ion or a structure in the active site for hydrogen bonds to form. A series of bishydroxamic acids were synthesized including suberic bishydroxamic acid (SBHA, Figure 2). This compound was two orders of magnitude more potent than HMBA.

To improve this structure and to pick up possible hydrophobic binding, a hydrophobic group was added to replace a hydroxamic acid in the SBHA chain. The reasoning behind this change was that if the molecule was coordinating with a metal, both ends would not bind at the same time therefore there was no need for two acids. The molecule synthesized was SAHA which was found to be six-fold more potent than the SBHA in causing transformed cell growth arrest and cell death. More potent variations of SAHA were synthesized such as one compound carrying two hydrophobic aromatic rings, but these were found to be too potent and toxic for a drug candidate. This was considered to be a key finding for the Breslow group. Other big pharma companies who had been working on this target were searching for the most potent compound which was all too toxic for therapeutic use. SAHA found a happy medium between potency and toxicity.

The inhibition of HDACs by SAHA was not realized until later when the similarity of SAHA to trichostatin A was recognized through a literature search by a student. A complex of SAHA and histone deacetylase-like protein (HDLP) was examined by X-ray crystallography. It was found that hydroxamic acid doubly coordinates to a zinc atom at the bottom of the cavity, the phenyl group at the other end fit on the hydrophic surface and the six-methylene chain fit through a narrow tunnel to get to the zinc atom. In conclusion, SAHA is a promising inhibitor of HDACs in a broad variety of transformed cells at doses that have relatively low toxicity.

Figure 2



“One-Pot Friedländer Quinoline Synthesis: Scope and Limitations”

Ti Wang, Department of Cancer Chemistry, OSI Pharmaceuticals, Inc., Farmingdale, NY

Friedländer synthesis is a very powerful and versatile tool for quinoline ring synthesis. This process is a one-pot synthesis using inexpensive reagents such as iron, HCl and KOH and is successful on a wide range of *o*-nitrocarbaldehydes and carbonyl compounds. This procedure works on a variety of ketones. Aliphatic and aromatic/heteroaromatic ketones were used along with an α,β -unsaturated ketone. Also an aldehyde can be used as the carbonyl component without self condensation (Table 1).

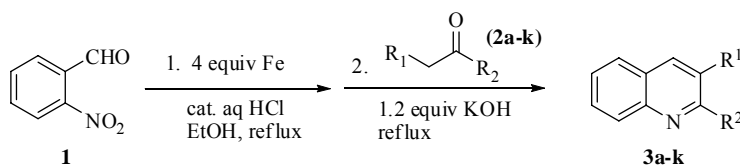


Table 1

Entry	R ¹	R ²	Product	Isolated yield, %
1	H	Ph	3a	99
2	H	Benzo[1,2]dioxoyl]	3b	70
3	H	2-Pyridyl	3c	92
4	H	1-Me-pyrrol-2-yl	3d	88
5	H	2-Thiophenyl	3e	80
6	H	<i>E</i> -Styryl	3f	77
7	H	<i>t</i> -Bu	3g	90
8	H	<i>o</i> -Pr	3h	91
9	H	CO ₂ Me	3i (R ² = CO ₂ H)	95
10	H	CH(OMe) ₂	3j	27
11	H	H	3k	87

Partial debromination was observed in entry 12 (Table 2) resulting in a lower yield. Strongly electron donating groups slow down the condensation step, likely due to the electron-rich ring reducing the electrophilicity of the aldehyde.

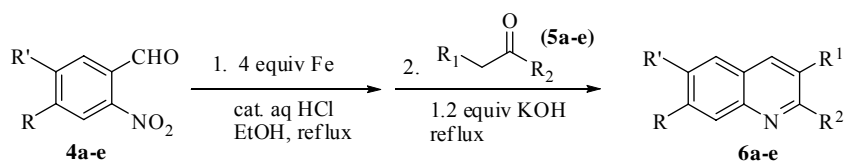


Table 2

Entry	R/R'	R ¹ /R ²	Product	Isolated yield, %
12	Br/H	H/Ph	6a	58
13	OCH ₂ O	H/Ph	6b	82
14	Me ₂ N/H	H/Ph	6c	67
15	CO ₂ Me/H	H/Ph	6d (R=CO ₂ H)	91
16	Cl/H	H/ <i>o</i> -F-Ph	6e	87
17	Cl/H	Me/Ph	6f	75
18	Cl/H	H/ <i>t</i> -Bu	6g	81
19	Cl/H	H/ <i>o</i> -Hex	6h	78