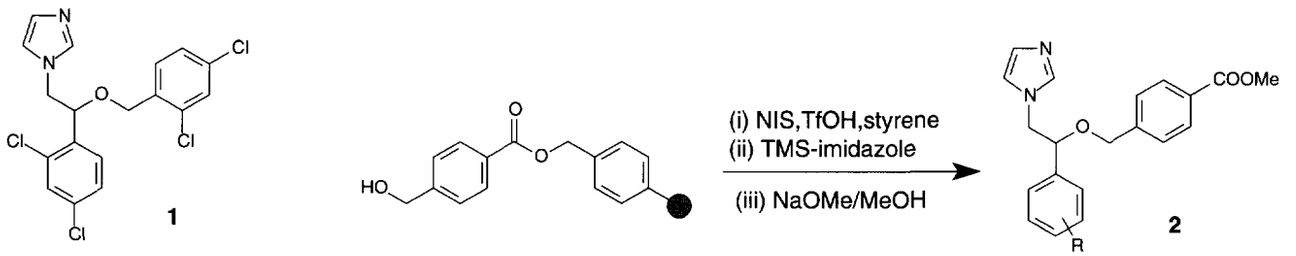

Scheme 1

range of styrenes in a key iodoetherification step. The iodoether product was derivatized with trimethylsilyl imidazole to give miconazole analogues (**2**) following cleavage with sodium methoxide (Scheme 1). A further extension of the work allowed displacement of the iodide with azide and subsequent reduction to give amines, which could then serve as a site for further diversification.

Although the yields from this route were low and variable, purities were generally high and the quantities produced were sufficient for biological assays. The route demonstrates the complexity of combinatorial synthesis currently achievable on solid-phase.

Resin capture methodologies

Armstrong has previously reported the concept of resin capture – a method by which a library synthesis commences in solution and a key intermediate is transferred to resin beads for the final step(s) [Keating, T.A. and Armstrong, R.W. *J. Am. Chem. Soc.* (1996) 118, 2574–2583]. This process effects a purification, because only suitably activated intermediates will react with the resin beads, and there is no build-up of side-products on the resin. Armstrong's group has used resin-capture for the synthesis of tetrasubstituted ethylenes related to tamoxifen (**3**) [Brown, S.D. and Armstrong, R.W. *J. Am. Chem. Soc.* (1996) 118, 6331–6332]. Bis(boryl)alkenes were monoarylated under Suzuki conditions and then captured with Rink resin-bound aryl iodide in a second Suzuki reaction, which proceeds without the addition of any further palladium catalyst (Scheme 2). The products were isolated as a mixture of regioisomers in >95% yield.

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Emerging molecular targets

RIIβ subunit of PKA and weight loss

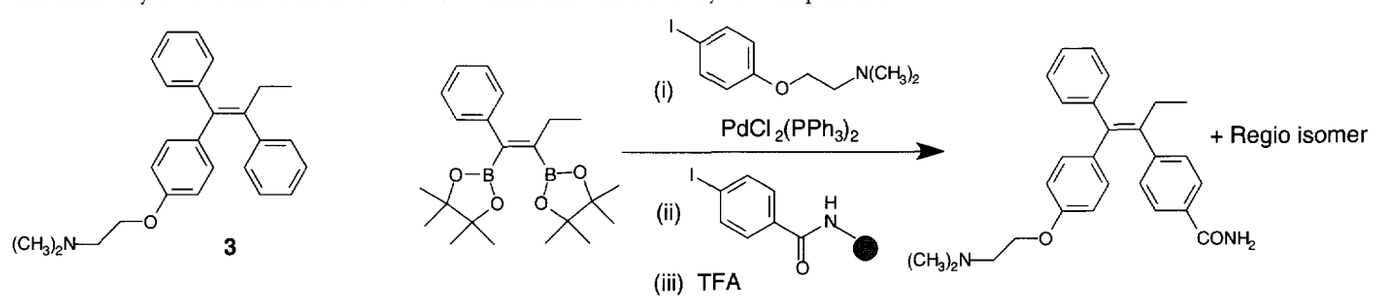
Protein kinase A is such a ubiquitous enzyme that it seems an unlikely molecular target for drug discovery of any kind, much less for anti-obesity drugs. But recent experiments from Stanley McKnight's laboratory at the University of Washington (Seattle, WA, USA) may suggest otherwise [*Nature* (1996) 382, 622–625].

Fat metabolism in adipocytes is highly regulated by protein kinase A (PKA) mediated phosphorylation. The RIIβ is the predominant regulatory subunit for PKA in brown fat, and the Seattle investigators wanted to know what would happen to fat metabolism if the RIIβ was depleted. They used targeted gene-disruption techniques to produce mutant mice that no longer produce the RIIβ subunit, and they found that the mice lost weight. The mutant mice had a body-fat composition of approximately 6% as compared to the 15% body-fat composition of the wild-type mice.

The explanation for the weight loss appears to reside in the tendency of the adipocyte to compensate for the loss of the RIIβ regulatory subunit by increasing synthesis of its isoform, the RIα subunit, which is normally present in brown fat only in very small amounts. The RIα subunit has a significantly higher affinity for cAMP than the RIIβ (K_d of 80 vs 350 nM). This results in a fivefold increase in the basal rate of activity for the mutant PKA compared with the wild-type enzyme. Overall, this causes a higher rate of basal metabolism, and much of the energy that would otherwise be stored as fat is dissipated as heat. The result is a leaner mouse.

When the wild-type mice were fed a high-fat diet over a four-month period, they became obese, while the mutant mice remained lean. But remarkably, the Seattle investigators found that the mice appeared normal in every other regard, maintaining normal plasma cholesterol, free fatty acid, insulin, glucose and thyroid hormone levels. Their results suggest that targeting the RIIβ subunit, or the transcriptional machinery that controls the ratio of the two regulatory subunits, might prove fruitful for the discovery of new anti-obesity drugs.

Robert W. Wallace



Scheme 2

1359-6446/96/$15.00