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The Preparation of Forskolin Analogs via Quinone Diels-Alder Reactions

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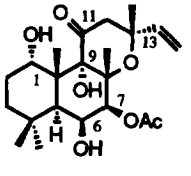
Abstract: A practical synthetic route for the preparation of compound 2a, a carbocyclic analog of the Δ^5-derivative, 1, of forskolin has been completed. A quinone Diels-Alder reaction is used for the rapid construction of the tricyclic framework of 2.

Forskolin is a labdane diterpene first isolated by de Souza, *et. al.* in 1977.[1] As a consequence of its unique ability to stimulate adenylyl cyclase (AC) it is a potent vasodilatory, hypotensive and inotropic agent.[2] The recent characterization and cloning of many different isoforms of AC,[3] including some that are relatively tissue-specific, presents the possibility that analogs of forskolin with far fewer side effects than forskolin itself might be found, due to subtype and, therefore, tissue selectivity. To this end, the synthesis of semi-synthetic forskolin derivatives has proven to be an attractive and expeditious route to the discovery of new and novel AC modulators.[4] However, very little work has been done on fully synthetic analogs of forskolin to ascertain precisely which parts of the natural product are essential for its AC activity. Thus, we sought to design simplified target molecules by considering the known structure-activity relationships (SAR) of forskolin and its derivatives as well as the practicalities imposed by the difficulties of synthesizing densely functionalized terpenes.



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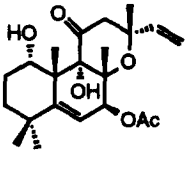

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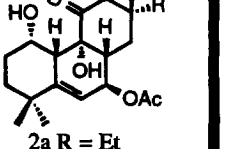
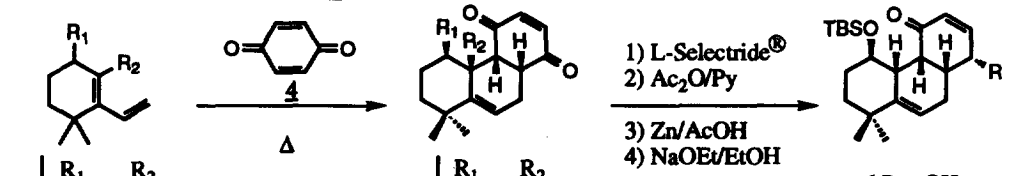


2a R = Et
2b R = Vinyl

Since the Δ^5-forskolin derivative, 1, retains the biological activity of forskolin[5] we hypothesized that this activity is due in large part to forskolin's ability to orient its C-1α and C-9α hydroxyls and the C-7β acetyl group correctly within its binding domain in the catalytic subunit of AC. Although compound 1 presents a simplified target molecule, additional modifications are clearly desirable in order to define targets that might eventually be amenable to rapid, large scale synthesis. Two changes that greatly reduce the synthetic complexity of structure 1, *and which are not precluded by known SAR*,[4] are the replacement of the C-8 and C-10 axial methyl groups by hydrogens and the replacement of the C-ring ether oxygen with a carbon atom. Furthermore, removal of the C-ring oxygen also improves the possibility that these agents will be more pharmacologically selective than forskolin, as this oxygen atom is believed to be required for glucose transporter activity.[6] The resulting target molecule is represented by structure 2, wherein

R is a vinyl or ethyl group. Substitution of an ethyl group for the vinyl substituent of forskolin causes only a five fold diminution of AC activity.

The tricyclic carbon skeleton of compound 2 is ideally suited for rapid construction via a Diels-Alder cycloaddition between a quinone and a vinyl cyclohexene, a reaction extensively studied by Engler.[7] In the context of the formal total syntheses of the tricyclic diterpenes taxodione and royleanone, Engler found that diene 3a, in the presence of a Lewis acid catalyst and/or 6-12 kbar of pressure, reacts with 1,4-benzoquinone, 4, to provide the endo cycloaddition adduct 5a.[7] Our synthesis requires 3b which, lacking a tetrasubstituted olefin, was expected to be a far more reactive Diels-Alder diene than 3a.



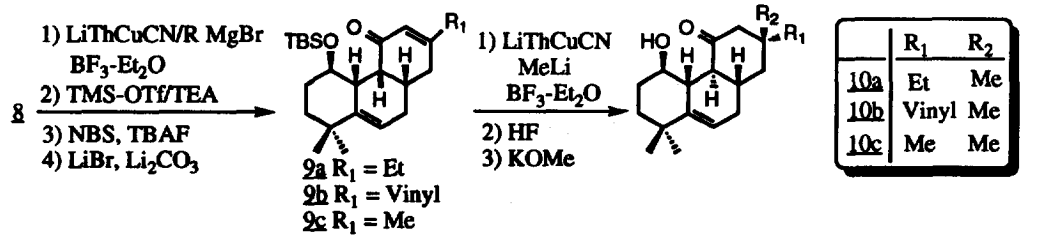
	R_1	R_2
3a	H	Me
3b	OTBS	H

	R_1	R_2
5a	H	Me
5b	OTBS	H

6 R = OH
7 R = OAc
8 R = H

In the event, diene 3b, prepared in four steps from 4,4-dimethyl-1,3-cyclohexanedione, reacts smoothly with 4 in refluxing toluene to provide the endo Diels-Alder adduct 5b in 60% yield.[8] The reactions of 2-methyl-1,4-benzoquinone, 2-ethyl-1,4-benzoquinone and 2,6-dimethyl-1,4-benzoquinone with diene 3b were also examined, but in each case the undesired regioisomeric Diels-Alder adduct was the major product. Attempts to affect the regiochemical outcome of these reactions through the use of Lewis acid catalysis resulted only in the destruction of diene.

The synthesis of compound 2 requires the C-14 carbonyl group of 5b to be reduced to a methylene unit. Thus, reduction of ene-dione 5b with L-Selectride® at -78°C occurs exclusively at the C-14 carbonyl group, from the less hindered convex face of the molecule, to give the C-14α alcohol 6. Deoxygenation of the resulting C-14 alcohol is accomplished in two steps by analogy with known steroid chemistry.[9] The alcohol is first acetylated with acetic anhydride in pyridine to give 7 in quantitative yield. Zinc/acetic acid reduction of the acetate then gives the intermediate β,γ-unsaturated ketone which, on exposure to sodium ethoxide in ethanol, isomerizes to provide a 74% yield of the α,β-unsaturated ketone 8.

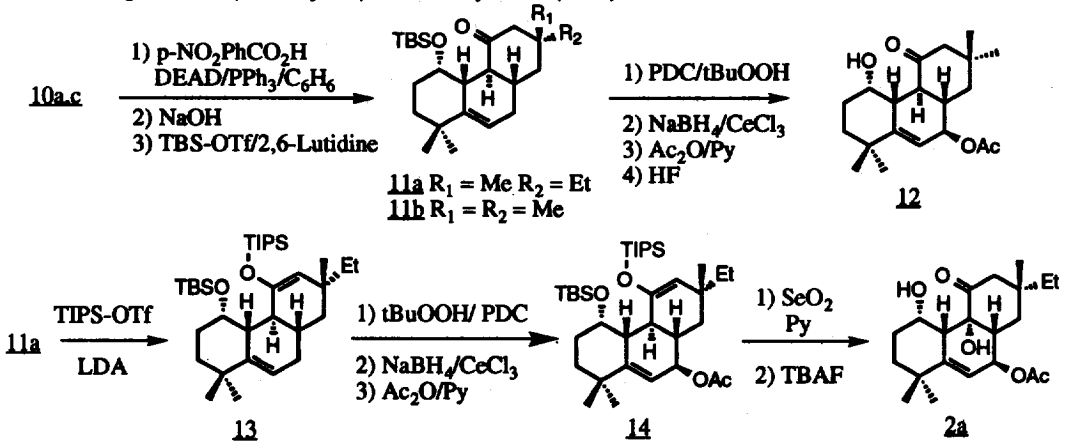


	R_1	R_2
10a	Et	Me
10b	Vinyl	Me
10c	Me	Me

Incorporation of the desired C-13 geminal dialkyl groups into enone 8 begins with addition of the higher order cuprate, generated from lithium-2-thienyl cyanocuprate and ethylmagnesium bromide, in the presence of BF_3-etherate[10] to give a quantitative yield of a single diastereomer,

presumably resulting from approach of the nucleophile from the less hindered convex face of the molecule. The enone functionality is then regenerated by the formation of the $\Delta^{11,12}$-TMS enol ether followed by reaction with N-bromosuccinimide/tetrabutylammonium fluoride to form the α-bromo ketone, and subsequent dehydrohalogenation with LiBr/Li_2CO_3 in refluxing DMF[11] to give 9a in 80% overall yield from 8. The cis B-C ring junction of 9a ensures that the next conjugate addition takes place exclusively from the less hindered β face of the molecule to give the desired stereochemistry at C-13. Thus, addition to 9a of the higher order cuprate derived from methyllithium, desilylation of the C-1 alcohol with HF and epimerization of C-9 then gives 10a in 63% yield. The vinyl derivative 9b is available by replacing ethylmagnesium bromide with vinylmagnesium bromide in the above sequence, but we were unable to add methylmagnesium bromide to 9b in a 1,4-fashion to give 10b. The C-13 dimethyl compound, 10c, is prepared analogously to 10a, with methyllithium replacing ethylmagnesium bromide in the synthesis of intermediate 9c.

With the trans-decalone in hand the C-1 alcohol of compounds 10a and 10c are inverted (room temp, 72h, 75%) under the modified Mitsunobu conditions developed by Martin for hindered substrates,[12] followed by reprotection of the C-1 hydroxyl as the TBS ether to give 11a-b in 85% yield. Compound 11b is then readily converted into the 9-deoxyforskolin analog, 12, by allylic oxidation (70% yield), selective reduction of the C-7 ketone (30-55% yield), acetylation of the resulting alcohol (100% yield) and desilylation (45%).



The problematic chemoselective reduction of the C-7 carbonyl in the presence of the C-11 carbonyl forced us to pursue a route to our target molecules in which the C-11 ketone, 11a, is protected as its enol ether, followed by oxidation at C-7. Initially we intended to insert the C-9 hydroxyl group via Rubottom oxidation of the $\Delta^{9,11}$-enol ether of 11a by analogy with previous work on the hydroxylation of 9-deoxyforskolin.[13] Silylation of 11a under various conditions failed to provide any of the desired $\Delta^{9,11}$-enol ether, but it gives good yields of the $\Delta^{11,12}$-enol ether. Thus, reaction of 11a with excess LDA and triisopropylsilyl triflate gives the TIPS enol ether 13 in 89% yield. Selective allylic oxidation at C-7 of 13 with t-BuOOH/PDC[14] then provides the C-7 ketone, albeit in only 31% yield. Alternative methods of allylic oxidation result in the undesired

conversion of the enol ether into the C-11 ketone. With the TIPS enol ether now serving as a protecting group for the C-11 ketone, the newly generated C-7 ketone is reduced with $NaBH_4/CeCl_3$ to give exclusively the β-C-7 alcohol which is then acetylated with acetic anhydride/pyridine to produce acetate 14 in 76% yield. Finally, in accord with the work of Khanelwal,[15] allylic oxidation of the enol ether functionality of 14 with SeO_2/py in refluxing dioxane,[16] followed by bis-desilylation with excess nBu_4NF gives the desired target molecule 2a in 41% yield.

In summary we have developed a practical synthetic route to analogs of the Δ^5-forskolin derivative, 1, in which the C-ring oxygen has been replaced by a carbon and the C-8 and C-10 axial methyl groups have been replaced with hydrogens. The ability of these compounds to stimulate adenylyl cyclase should provide valuable information on the structure-activity relationships of forskolin and will be reported in due course.

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