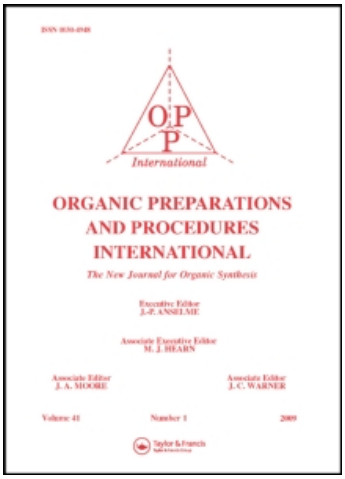

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SYNTHESIS OF QUASSINOIDS. A REVIEW

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SYNTHESIS OF QUASSINOIDS. A REVIEW

Kenji Kawada, Moonsun Kim and David S. Watt*

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University of Kentucky, Lexington, KY 40506

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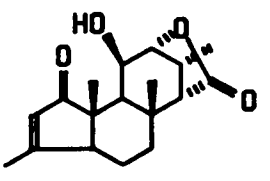
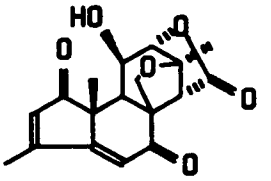
INTRODUCTION

The quassinoids represent a structurally complex group of degraded triterpenes that possess a number of different C_{18}, C_{19}, C_{20}, and C_{25} skeletal types as illustrated by the representative examples in Scheme 1. The C_{20} picrasane skeleton

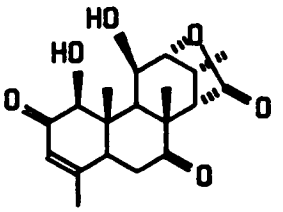
Scheme 1



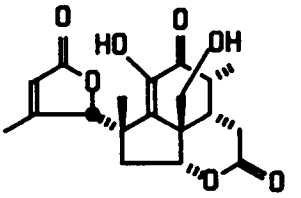
laurycolactone A (1)



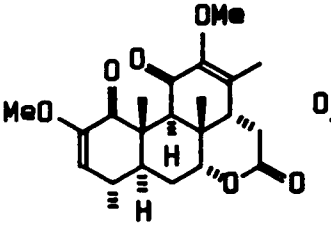
samaderine A (2)



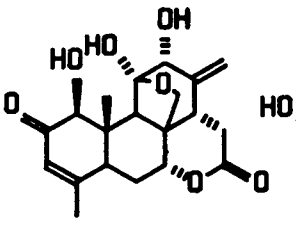
eurycomalactone (3)



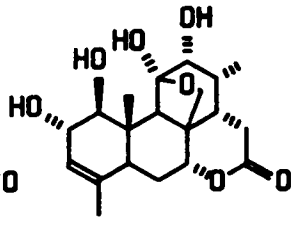
shinjulactone B (4)



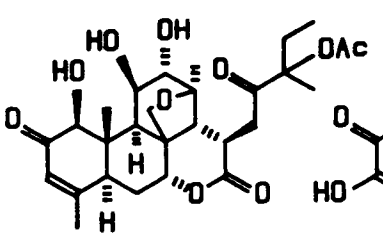
quassin (5)



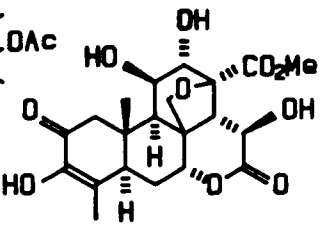
ailanthone (6)



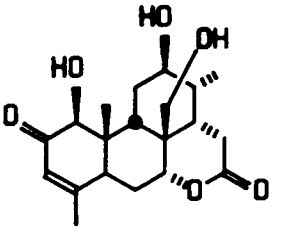
chaparrin (7)



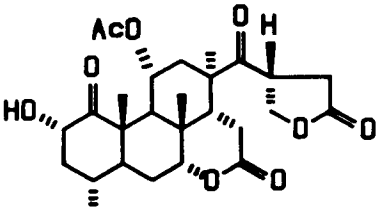
quassimarin (8)



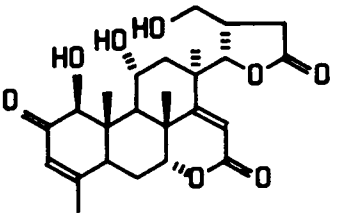
bruceolide (9)



shinjulactone C (10)



simarolide (11)



soulameolide (12)

exemplified by quassin (5) occupies a prominent position among the quassinoids for its numerical superiority, diverse functionality, and biological activity and constitutes the primary focus of this review. Excellent reviews by Polonsky[1] summarize both the chemical history of quassinoid structure elucidation, the chemical diversity of the members of this group, and a brief overview of synthetic efforts in this area.

The concatenation of carbocyclic and heterocyclic rings and the dense array of functional groups attracted the interest of synthetic chemists beginning with the seminal work by Graf[2] on the partial synthesis of quassinoids from steroids and by Valenta[3] on the total synthesis of quassin (5), the tetracyclic namesake of this family of natural products. Additional discoveries that the pentacyclic quassinoids in the picrasane family possessed a spectrum of biological activities including antiviral, antiparasitic, insecticidal, antifeedant, anti-ameobicidal, and anti-inflammatory activity[1] further spurred the development of synthetic pathways to these natural products. This review will provide a detailed perspective on

the synthetic achievements in the quassinoid area through April of 1989.

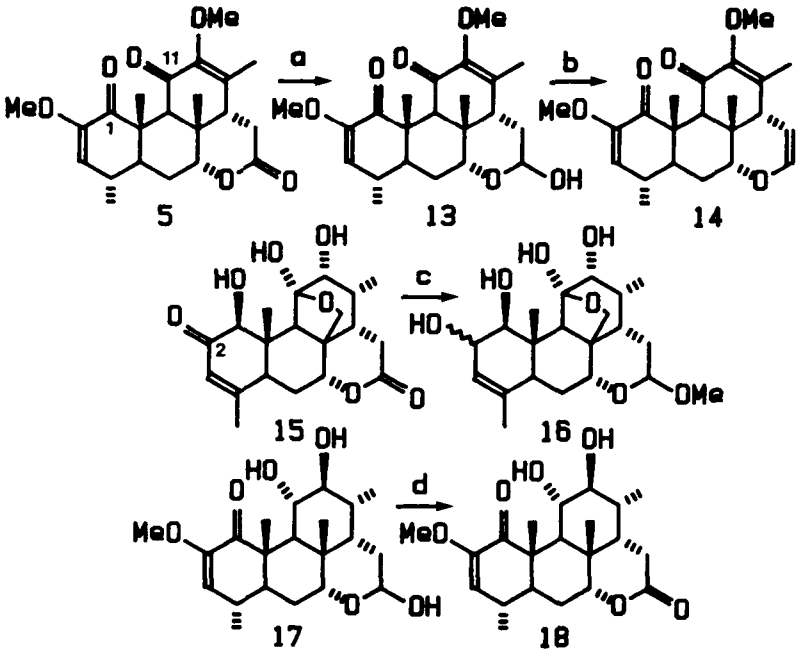
I. QUASSINOID REACTIONS

The rationale for the partial syntheses of various quassinoids resided in a desire either to confirm a structural assignment in the era that preceded high resolution FT NMR methods, to test synthetic methodology needed as part of a total synthesis, or to obtain relatively rare quassinoids for biological evaluation from their more common counterparts. The legacy of these investigations provide critical information for the practitioner of total synthesis by unveiling the chemical behavior of the polyfunctional quassinoids and thereby guiding synthetic planning. In this review, we will focus briefly on selected reactions of the quassinoids that highlight the acid- and base-catalyzed epimerizations and rearrangements, certain functional group interconversions, and the susceptibility of the quassinoids to oxidation and reduction.

a. δ-Lactol and δ-Lactone Interconversions

The δ-lactone, which represents a ubiquitous structural feature of the C_{20} and C_{25} quassinoids, undergoes typical reduction, saponification, and transacylation with proximal hydroxyl groups. The former reaction, illustrated by the interconversion of quassin[4] (5) and neoquassin (13) in Scheme 2, suggested that the conversion of a quassinoid δ-lactone to

Scheme 2



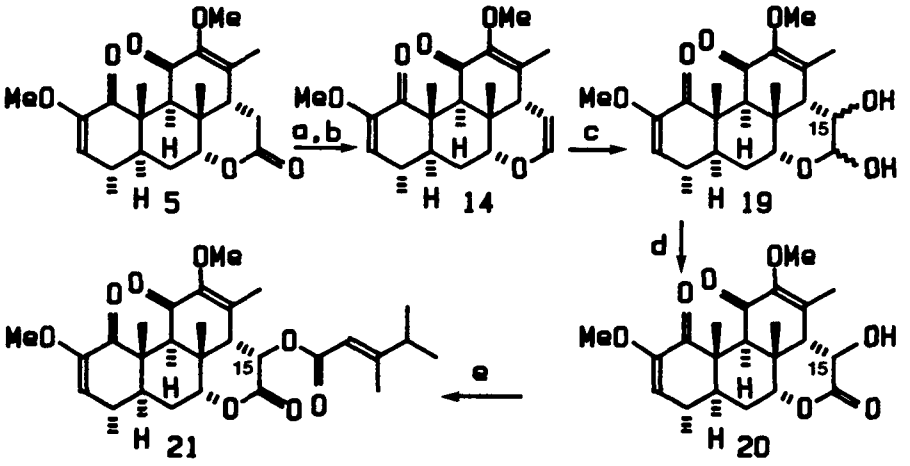
a) $NaBH_4$ b) Ac_2O c) $NaBH_4$, MeOH d) Ag_2O

a protected δ-lactol was an obvious means for preventing saponification and rearrangement of the δ-lactone in the course of a total synthesis. The sodium borohydride reduction of the δ-lactone in quassin[4] (5) and chaparrinone[5] (15) provided the corresponding lactols or the methyl acetals, exhibited some regioselectivity in the presence of hindered C-1 and C-11 keto groups, but as expected, reduced accessible ketones as in the reduction of the C-2 ketone in 15. The stability of the protected δ-lactols toward nucleophiles proved useful in the successful total syntheses of quassin, castanolide, and klaineanone that will be described shortly. The selective re-oxidation of a quassinoid δ-lactol to a δ-lactone presumably drew from examples such as those of Takahashi who demonstrated that the oxidation of nigakihemi-

acetal A[6], B[6], and C[7] (17) provided nigakilactone F, quassin (5), and nigakilactone A (18), respectively.

The dehydration of δ-lactols to dihydropyrans, as illustrated in Scheme 2 by the conversion of neoquassin (13) to anhydroneoquassin[4] (14), suggested a route for obtaining the α-hydroxy-δ-lactones and α-acyloxy-δ-lactones characteristic of various quassinoids such as bruceolide (9) and quassimarin (8) in Scheme 1. In an effort to correlate biological activity and certain structural features of the quassinoids, Takahashi[8a,b] examined the conversion of quassin (5) to a C-15β acyloxy-substituted quassin 21 as shown in Scheme 3,

Scheme 3

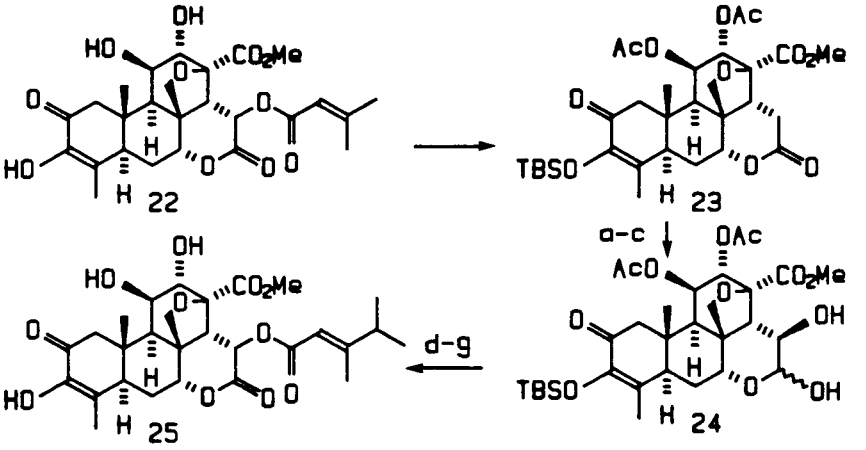


a) $NaBH_4$, EtOH b) HMPA c) OsO_4, Py followed by aq. $NaHSO_3$ d) Ag_2O e) (E)-3,4-dimethyl-2-pentenoyl chloride, K_2CO_3

that employed a dihydropyran intermediate. The sodium borohydride or diisobutylaluminum hydride reduction[4] of 5 to neoquassin and dehydration of the δ-lactol provided the dihydropyran 14. A selective osmium tetraoxide oxidation of 14 and a silver oxide oxidation of 15β-hydroxyneoquassin (19)

furnished 15β-hydroxyquassin (20). Acylation of 20 with 3,4-dimethyl-2-pentenoyl chloride completed the sequence. In a related study shown in Scheme 4, Murae[8c] reported the

Scheme 4



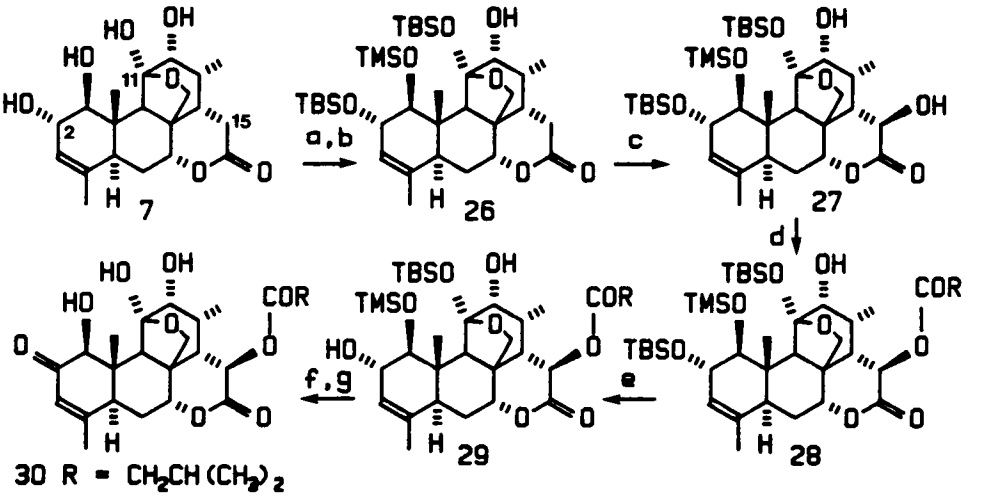
a) $NaBH_4$ b) $POCl_3$, Py c) MCPBA, aq. $NaHCO_3$, CH_2Cl_2 (61%) d) Ag_2O e) aq. HO^- f) (E)-3,4-dimethyl-2-pentenoyl chloride, DCC, DMAP (72%) g) 3N H_2SO_4, MeOH (15%)

conversion of the lactone 23 derived from brusatol (22) to bruceantin (25) that employed a similar dihydropyran intermediate but effected the oxidation to the α-hydroxy-δ-lactol 24 using m-chloroperoxybenzoic acid in a two-phase, aqueous sodium bicarbonate and dichloromethane medium.

In 1982, Polonsky,[9] who has contributed much of her career to unraveling the chemistry of the quassinoids, reported the conversion of the biologically inactive chaparrin (7) to castelanone (30). Although the motivation for this study was to provide an adequate supply of 30 for biological evaluation, this investigation also reported another procedure for the introduction of the C-15β acyloxy group and is included here for comparison purposes. The key features of this

interconversion were the need to oxidize the C-15 position as well as the the C-2α allylic alcohol in 7 without cleaving the C-1,2 bond. As shown in Scheme 5, tackling the former

Scheme 5



a) t-BuMe$_2$SiCl, imidazole (88%) b) Me$_3$SiOTf, Py (100%) c) LDA, MoOPH d) i-C$_4$H$_9$COCl, Py, CH$_2$Cl$_2$ (57%) e) 1M HCl, MeOH f) Jones' (80%) g) n-Bu$_4$NF, THF (30-45%)

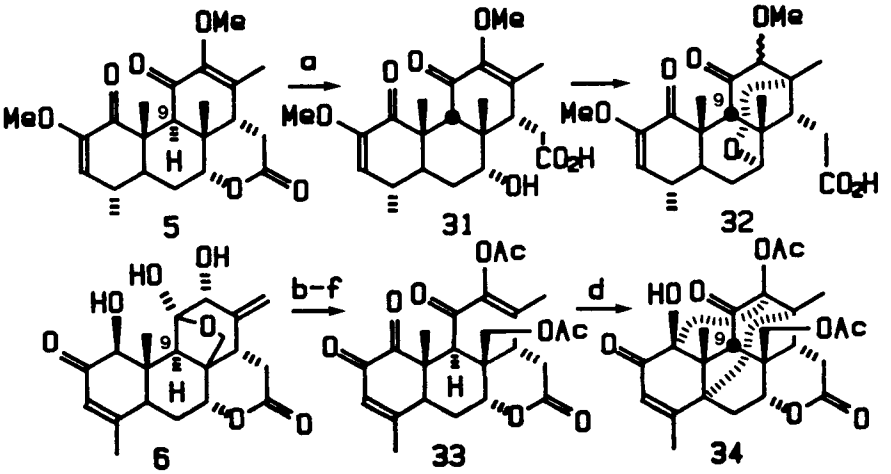
objective first required the protection of the C-1, C-2, and C-11 hydroxyl groups and the subsequent oxidation of the δ-lactone enolate using Mimoun's reagent[10] (MoOPH) in order to obtain the α-hydroxy-δ-lactone 27. Efforts to deprotect the silyl ethers using tetra-n-butylammonium fluoride led to mixtures, but fortunately, the selective deprotection of the C-2α allylic silyl ether was achieved with hydrochloric acid in methanol. Jones' oxidation and deprotection led to 30.

b. C-9 Stereochemistry

With the possible exception of shinjulactone C (10) in Scheme 1, the quassinoids possess a trans-fused BC ring system with the C-9α(H) stereochemistry. In various total syntheses

that we will describe shortly, a number of investigators employed a Diels-Alder strategy for assembling the BC rings of the quassinoid skeleton. This approach led, by necessity, to the cis-orientation of the C-9 hydrogen and the C-8 angular substituent in the adduct and required the subsequent epimerization of the C-9β(H) center relative to a C-8β angular substituent to arrive at the natural C-9α(H) stereochemistry. Although the C-9α(H) configuration is preferred thermodynamically, it is possible to intercept the C-9β(H) epimer under circumstances where a new bond forming reaction locks the cis-fused BC rings. Among the first of such examples was the base-catalyzed conversion of quassin (5) to pseudoquassinolic acid[4] (32) in Scheme 6. Saponfication of the δ-lactone and

Scheme 6



a) 10% aq. NaOH b) TBSCl, imidazole, DMF c) Ac_2O, Py d) Py, reflux e) HOAc, aq. THF f) Jones' oxidation

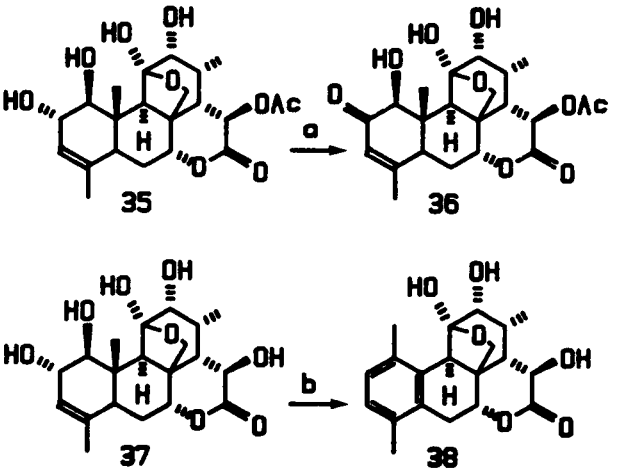
epimerization at C-9 permitted a Michael-type addition of the C-7α hydroxyl group to C-13 thereby freezing the C-9β(H) stereochemistry in place. A considerably more dramatic example[11] of a C-9 epimerization involved the conversion of

ailanthone (6) to the enedione 33 that rearranged in refluxing pyridine to the diacetate (34) of shinjulactone C. The intramolecular Michael addition of the C-5 enolate to the diosphenol in the C ring of 33 led to a C-12 enolate that in turn added to the C-1 keto group to complete construction of the transannular C-1,12 and C-5,13 bonds of 34.

c. Enediol Interconversions

A number of the quassinoids possess either the enediol functionality as in chaparrin (7) or the α'-hydroxyenone functionality as in quassimarin (8). Among the reactions characteristic of the enediol functionality are the allylic oxidation illustrated by the conversion of glaucarubin[12] (35) to glaucarubinone (36) in Scheme 7 and the acid-catalyzed

Scheme 7

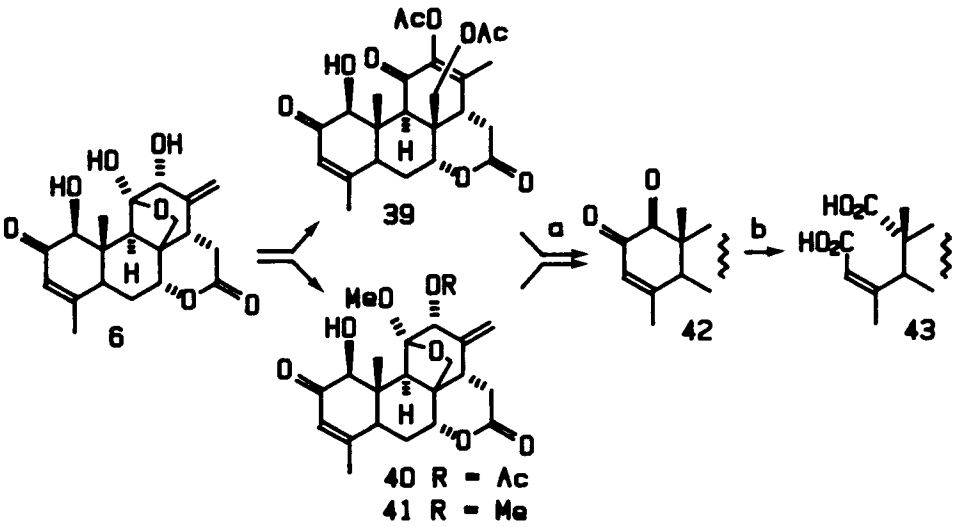


a) MnO_2 b) 1N HCl

aromatization of the A ring illustrated by the conversion of glaucarubol[13] (37) to glaucanol (38). In a study directed toward the 1,2-seco-1-nor-6(5-10)-abeo-picrasane skeleton of shinjulactone B (4) in Scheme 1, Tsuyuki[14] also examined the

oxidative degradation of the A ring of ailanthone (6) in Scheme 8, that provided some insight as to the stability of

Scheme 8



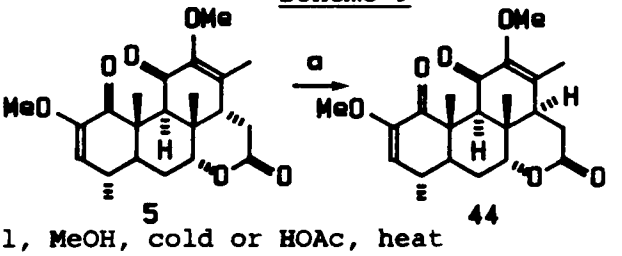
a) Jones' oxidation b) 30% H_2O_2, HOAc

the α'-hydroxyenone functionality. It was possible to oxidize ailanthone derivatives 39, 40, or 41 using Jones' reagent to secure the enediones 42, and exposure of 42 to acidic hydrogen peroxide ruptured the C-1,2 bond leading to the diacids 43.

d. C-14 Stereochemistry

Although relatively rare, the epimerization of the C-14β(H) position in certain quassinoids constitutes another process that could intervene in the course of a total synthesis. As illustrated in Scheme 9, heating quassin[4] (5) in

Scheme 9



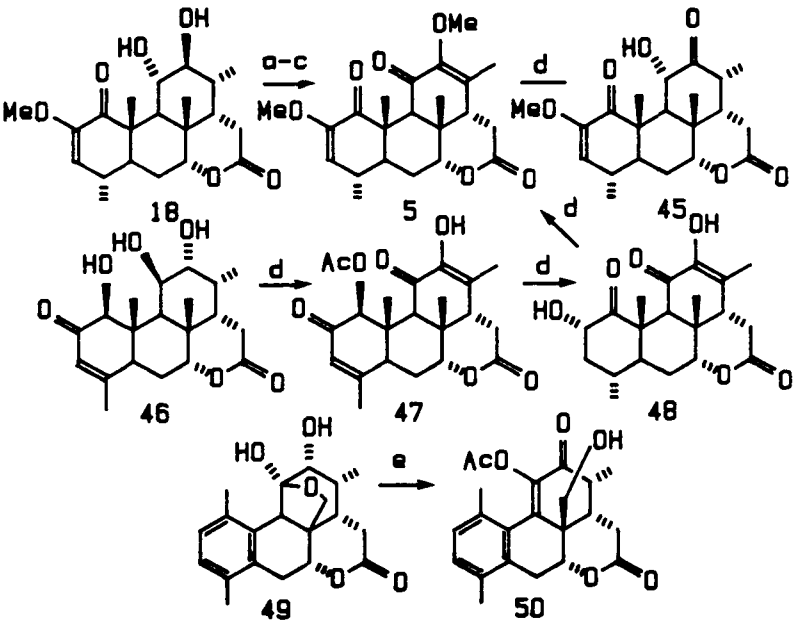
a) HCl, MeOH, cold or HOAc, heat

acetic acid or treating 5 with cold methanolic hydrogen chloride led to isoquassin (44) as a result of the enolization of the O-methyldiosphenol functionality.

e. Diol, α-Ketol and Diosphenol Interconversions

The oxidation of diol and α-ketol functionality in the A and C rings of various quassinoids to the diosphenol oxidation level was a common procedure employed to interrelate the rare quassinoids such as nigakilactone A[15] (18) and similakalactone C[1] (45) with the well known quassinoids such as quassin (5) as shown in Scheme 10. Other less direct interconversions such

Scheme 10



a) CrO_3, Py b) Bi_2O_3 c) Me_2SO_4 d) see reference 1 e) $Bi(OAc)_3$

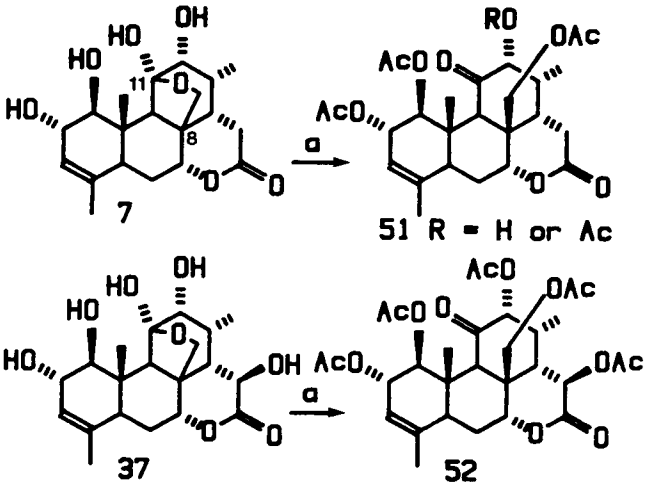
as that of klaineanone[16] (46) to quassin (5) or chaparrol[17] (49) to the O-acetyldiosphenol 50 illustrate typical applications of bismuth(III) reagents[18] for the oxidation of α-ketols

to diosphenols. Subsequent work[19] led to the adoption of the Swern oxidation[20] to achieve similar results.

f. Oxymethylene Bridge Rupture

Acetylation of quassinoids possessing a C-8,11 oxymethylene bridge as part of a hemiketal structure as in chaparrin[17] (7) and glaucarubol[21] (37) in Scheme 11 led to the ring-opened

Scheme 11



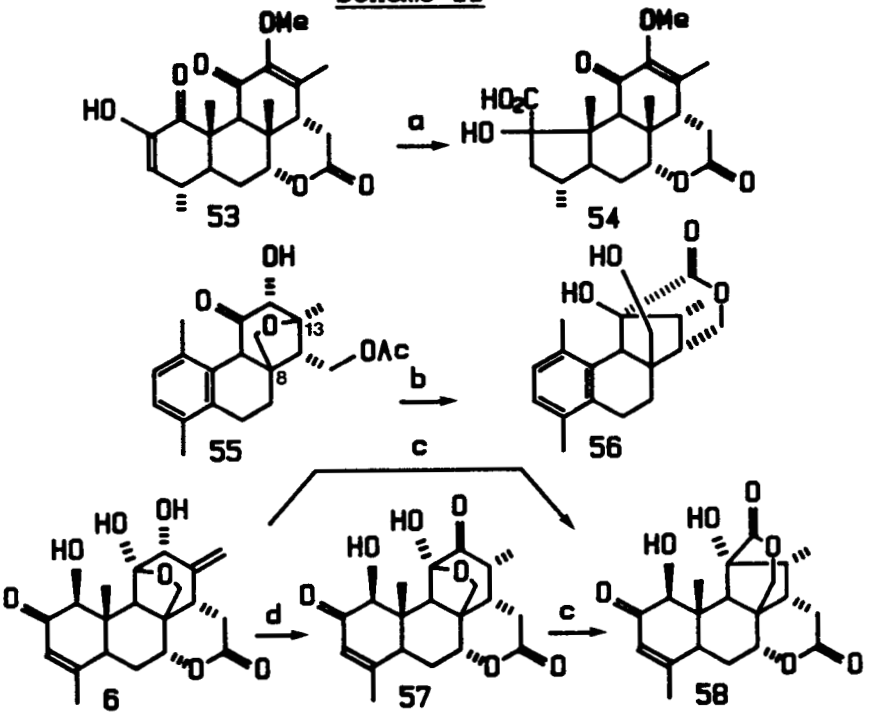
a) Ac_2O, Py

keto acetate derivatives 51 and 52, respectively. Another similar ring opening was also presented in Scheme 6 in connection with the conversion of ailanthone[11] (6) to the diacetate 34 of shinjulactone C.

g. Benzilic Acid Rearrangements

Quassinoids that possessed diosphenol functionality exhibited the benzilic acid rearrangement involving ring contraction to an α-hydroxyacid. A recently discovered member of the quassinoid family, shinjudilactone[22,23] (58) in Scheme 12, possessed a contracted C ring which suggested the inter-

Scheme 12



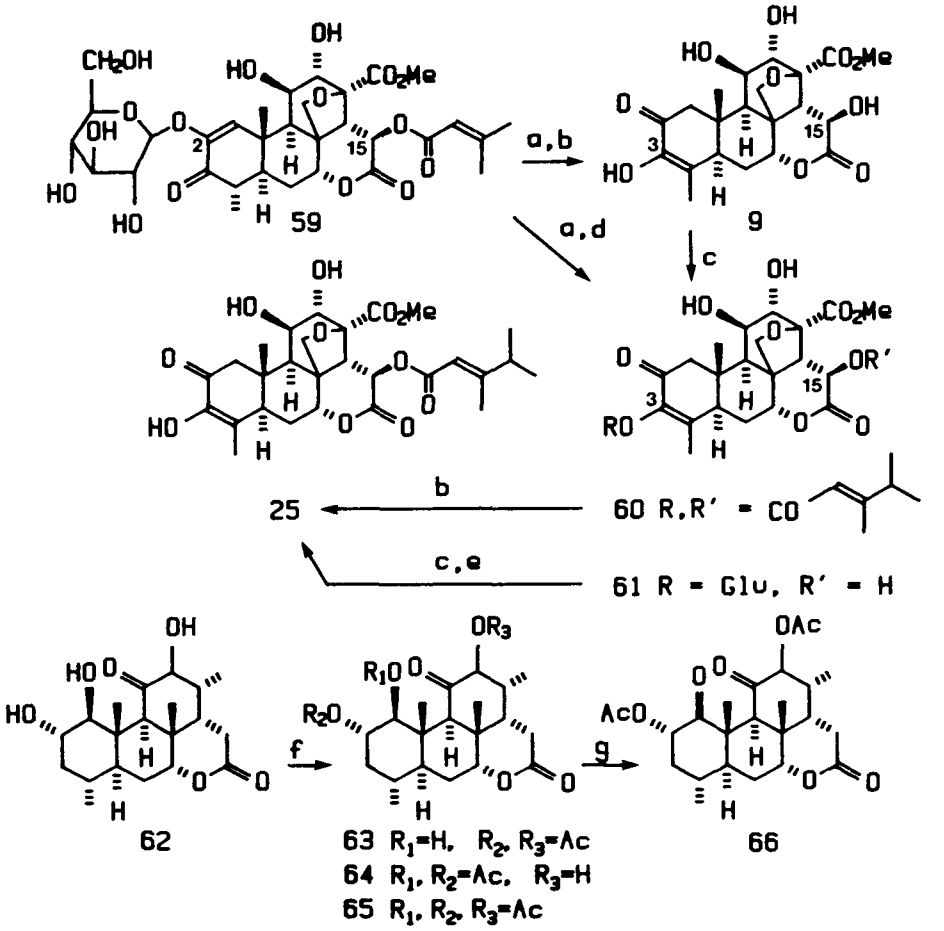
a) 10% aq. NaOH, reflux b) see reference 24 c) $NaHCO_3$, aq. MeOH, reflux followed by HCl d) Py, heat

vention of an analogous rearrangement in the biosynthetic pathway. The base-catalyzed conversion of norquassin[4] (53) to norquassinic acid (54), as illustrated in Scheme 12, is an archetypical example of this process. As an additional, somewhat convoluted example,[24] the β-elimination of the C-8,13 oxymethylene bridge in 55, benzilic acid rearrangement, and lactonization gave the C ring-contracted α-hydroxyacid 56. Another benzilic acid rearrangement[22] in which the ring opening of the hemiketal in ailanthone (6) and subsequent isomerization of the exocyclic methylene generated the α-keto hemiketal 57, and in turn, this intermediate suffered ring opening of the hemiketal, rearrangement, and lactonization to give shinjudilactone (58).

h. Selective Esterification of Hydroxylated Quassinoids

As shown in Scheme 13, in a study undertaken to provide a

Scheme 13



a) 1M KOH, MeOH b) p-TsOH, MeOH c) (E)-3,4-dimethyl-2-pentenoyl chloride, Py d) CH_2N_2 e) $BF_3 \cdot Et_2O$, CH_2Cl_2 f) Ac_2O, Py g) Jones' oxidation

critical supply of bruceantin (25) for clinical evaluation, Lee[25] studied the interconversion of bruceoside A (59) to 25 and defined the relative reactivity of the C-15 hydroxyl group relative to the 11β,12α-diol characteristic of many of the quassinoids. The successive hydrolysis of the C-15 senecioyl

ester and the C-2 glucoside in 59 furnished bruceolide (9). Preferential acylation of the C-3 and C-15 hydroxyl groups in 9 using (E)-3,4-dimethyl-2-pentenoyl chloride in the presence of the C-11β,12α diol provided the diester 60, and an acid-catalyzed hydrolysis of the C-3 enol ester functionality completed the approach to 25. Success with this approach suggested that the C-2 glycoside itself might serve to protect the A ring diosphenol, and in a second approach,[25] an esterification of the C-15 hydroxyl group (as well as the glucose hydroxyl groups) in 15-desenecioyl bruceoside A (61) using (E)-3,4-dimethyl-2-pentenoyl chloride followed by an acid-catalyzed hydrolysis again furnished 25. The ability to differentiate the various hydroxyl groups in 9 by selective acylation is, however, not always realized in other quassinoids as illustrated by the acetylation[26] of chaparrolide (62) to give a 1:1.6:1.9 ratio of 63, 64, and 65, respectively.

III. QUASSINOID SYNTHESES

Since relatively few of the synthetic efforts in the quassinoid area have culminated in completed syntheses, we adopted the practice of including those synthetic efforts that delineated a solution to a particular structural feature common to the quassinoids or defined the problems associated with a particular strategy for assembling the quassinoids. We have, for purposes of organization, arbitrarily subdivided these synthetic efforts into those directed toward racemic products or directed toward a specific enantiomer. These efforts were further subdivided into the tetracyclic and

pentacyclic quassinoid families with subheadings that indicate the order in which the various rings were introduced. This organizational scheme succeeds in large measure because most of the synthetic effort has focused on the C_{20} picrasane skeleton despite the variety of quassinoid skeletal types indicated in Scheme 1. In order to identify the ultimate positions of the carbons in the starting materials and intermediates in the various syntheses, we adopted the picrasane numbering scheme throughout the discussion and labeled the carbocyclic and heterocyclic rings to fit the standard ABCDE pattern in the quassinoids. The picrasane numbering scheme is reproduced in structure 67.

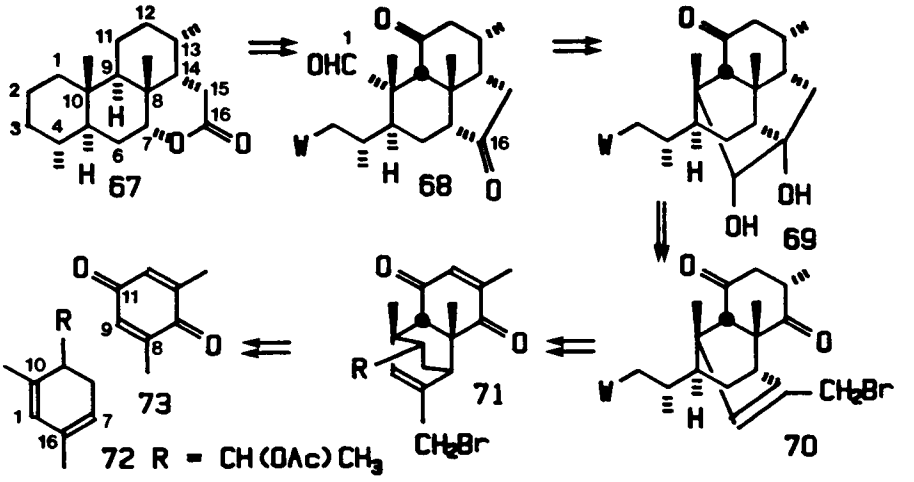
a. Synthetic Ventures Using Racemic Intermediates

1. Tetracyclic Skeleton

(a) C-BC-BCD....ABCD Approach

One of the original and most imaginative assaults on the tetracyclic quassinoid, quassin (5), was reported by Valenta.[3] Although this particular approach never reached fruition in terms of a completed synthesis of a natural quassinoid, this contribution was to herald the subsequent investigations by others in which the Diels-Alder reaction was to assume a prominent role for the assembly of cis-fused BC rings. A brief retroanalysis of the Valenta route[3] to the picrasane skeleton 67 revealed that the initial subgoal of the synthesis was the preparation of an intermediate 68 bearing an aldehyde group at C-1, the unnatural C-9β(H) stereochemistry, and a cyclopentanone D ring that would serve as a progenitor of the δ-lactone, as shown in Scheme 14. The cis-fusion of the BC

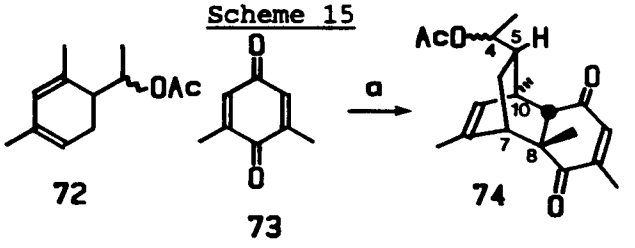
Scheme 14

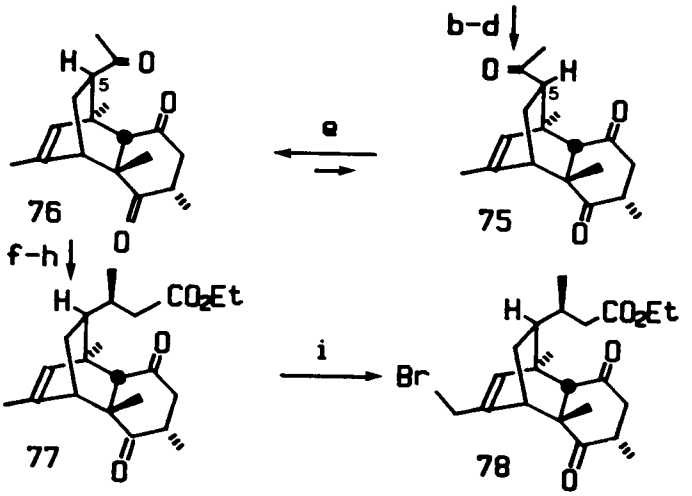


rings in 68 would place both the C-1 aldehyde and the C-16 carbonyl of the cyclopentanone in close proximity for connection as the diol 69. The further disconnection of the C-14,15 bond in 69 generated the tricyclic system in which the bicyclo[2.2.2]octene subunit was apparent, and the recognition of this subunit suggested the Diels-Alder foundation on which the synthesis was based. Clearly, this particular avenue to the quassinoids selected starting materials that so disguise the ultimate position of these carbons of the quassinoid framework that the accolade, "imaginative" is, in this instance, fully deserved. It is instructive, for example, to compare the positions of the carbons in the diene 72 relative to their ultimate positions in the picrasane skeleton 67.

The synthetic effort, presented in Scheme 15, began with

Scheme 15





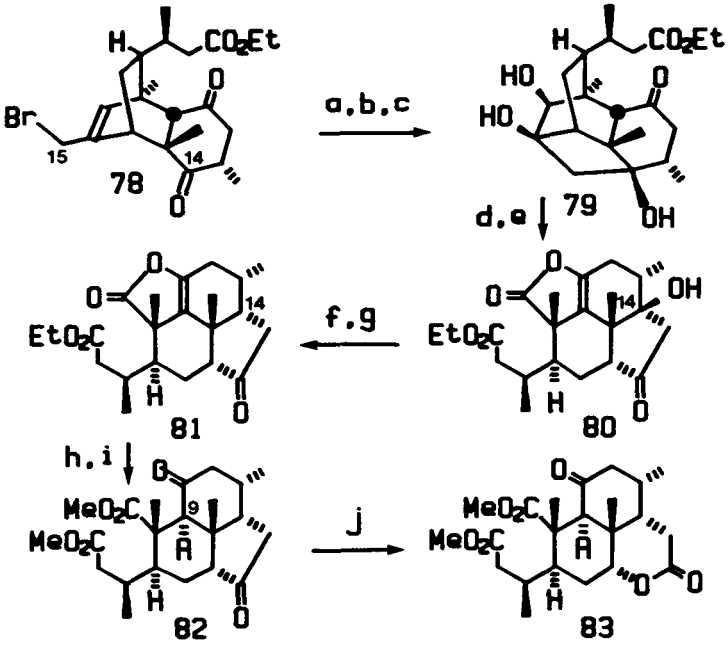
a) $BF_3 \cdot Et_2O$ b) Zn, HOAc c) HCl, MeOH d) $CrO_3 \cdot 2Py$ e) K_2CO_3, MeOH f) EtOC≡CMgBr g) $(CO_2H)_2$, EtOH h) H_2, PtO_2 i) NBS

a Lewis acid-catalyzed Diels-Alder reaction between the cyclohexadiene 72 and the dienophile, 2,6-dimethyl-1,4-benzoquinone (73), that led to the adduct 74 with key stereochemical positions at C-7, C-8, and C-10 established within a rigid polycyclic framework. In this cycloaddition, the boron trifluoride catalyst directed the addition in a mode contrary to the usual regiochemical preference, and steric factors guided the facial selectivity. With three of the five desired B ring stereocenters in place, Valenta[3] next addressed the problem of epimerizing the C-5 position. Reduction of the enedione group in the adduct 74, conversion of the C-4 acetate to a ketone, and epimerization of ketone 75 gave a 3:2 ratio of the desired ketone 76 and the original ketone 75. Attention then shifted to the addition of the remaining carbons that would eventually become part of the A ring prior to the introduction of the fifth C-9 stereocenter. A two-carbon homologation of the ketone 76 using 1-ethoxy-2-ethynylmagnesium bromide furnished

the carboxylic ester 77 and the bromination of the vinylic methyl group with N-bromosuccinimide provided the allylic bromide 78.

As shown in Scheme 16, a stereospecific addition of

Scheme 16



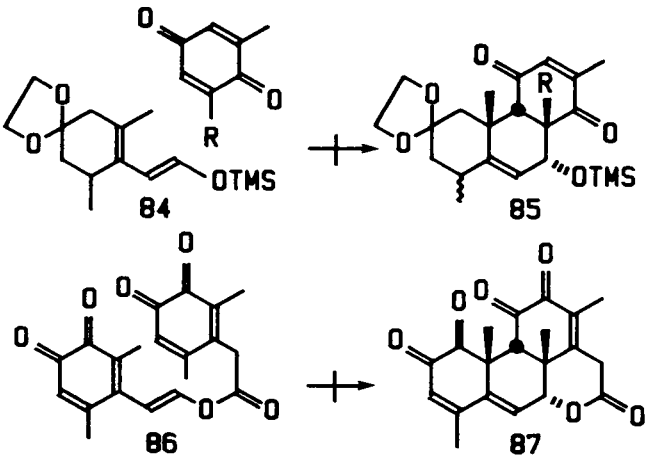
a) OsO_4 b) Zn, HOAc c) H_2S d) H_5IO_6 e) $CrO_3 \cdot 2Py$ f) Ac_2O, Py g) H_2, PtO_2 h) NaOMe, MeOH i) CH_2N_2 j) CH_3CO_3H

osmium tetroxide to the allylic bromide 78 set the stage for the closure of the C-14,15 bond. Reduction with zinc promoted a cyclization between C-14 and C-15 that, after reduction of the osmate ester, provided triol 79. Periodate cleavage of the vicinal diol in 79 afforded the tetracyclic lactone 80, an intermediate with recognizable B, C, and D rings of a quassinoid. Elimination of the C-14 tertiary alcohol in lactone 80 followed by the stereoselective hydrogenation of the resulting enone from the β-face gave ketone 81 with the correct C-14β(H)

stereochemistry of quassin (5). Base-catalyzed opening of the lactone in 81 gave the ester 82 with the correct C-9α(H) stereochemistry. A selective Baeyer-Villiger oxidation of the cyclopentanone in 82 provided the lactone 83, an attractive intermediate for the synthesis of tetracyclic quassinoids.

Other investigators unsuccessfully examined approaches that are conceptually related to Valenta's route. As shown in Scheme 17, Takahashi[8b] studied a variation that required the

Scheme 17



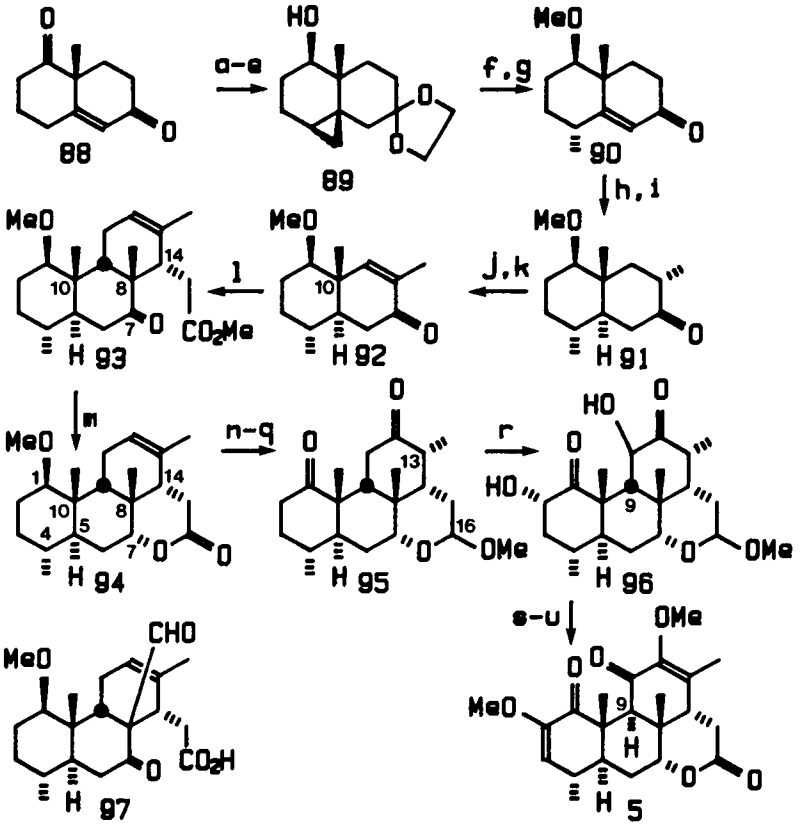
addition of a benzoquinone dienophile and a vinylcyclohexene 84 in an effort to obtain a tricyclic adduct 85. However, only tetracyanoethylene would react with the hindered diene 84. Mandel[27,28] unsuccessfully explored an intramolecular version involving the bis(orthoquinone) 86.

(b) A-AB-ABC-ABCD Approach

Few groups have contributed as much to the development of viable routes to the quassinoids than that of Grieco and coworkers.[29-32] A series of imaginative studies culminating in the synthesis of racemic quassin,[30] castelanolide,[31] and

klaineanone[32] began with a report[29a] describing the aluminum trichloride-catalyzed Diels-Alder reaction of the bicyclic enone 92 with a deconjugated sorbate ester shown in Scheme 18.

Scheme 18



a) $NaBH_4$ b) Ac_2O, Py c) EG, 2-naphthalenesulfonic acid (68%) d) $LiAlH_4$ e) Zn-Cu, CH_2I_2 f) NaH, MeI, n-Bu_4NI g) 70%, $HClO_4$, CH_2Cl_2, 0° h) LDA, MeI i) Li, NH_3 j) $PhN(CH_3)_3Br_3$ k) Li_2CO_3, LiBr, DMF, 140° l) $AlCl_3$ (0.25 eq), $CH_2{=}CHC(CH_3){=}CHCH_2CO_2CH_3$ (40%) m) $NaBH_4$, MeOH (89%) n) $BF_3{\cdot}Et_2O$, $HSCH_2CH_2SH$ (82%) o) DIBAL, -78° followed by HCl, MeOH p) B_2H_6 followed by NaOH, H_2O_2 q) $CrO_3{\cdot}2Py$ r) LDA, MoOPH, 0° (35%) s) NaOMe, DMSO followed by MeI (50%) t) HOAc, H_2O, heat u) Ag_2CO_3/Celite

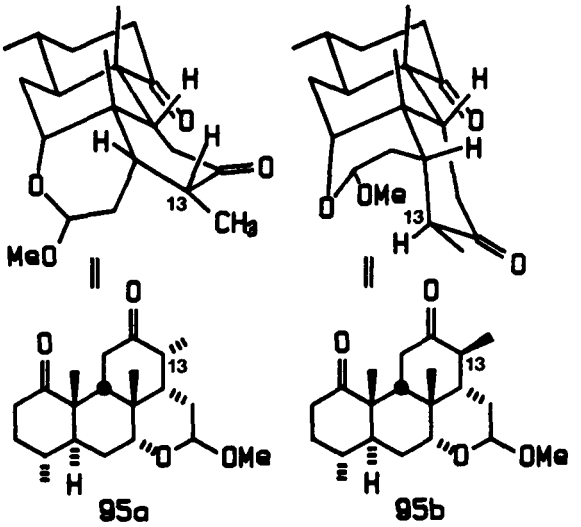
The enone 92 was prepared, in turn, through a sequence[33] originating with the Wieland-Miescher ketone 88. This Diels-Alder

reaction relied on the C-10β angular methyl to direct the diene to the α-face of 92 and provide 93 with the correct syn-relationship between the C-8 and C-10 angular methyl groups. The ketone 93 was obtained as a 1:1.2 mixture of C-14β(H) and (undesired) C-14α(H) epimers in 52% yield, but in subsequent investigations[29c,d] using an aqueous Diels-Alder reaction of the sodium salt of the deconjugated sorbate, Grieco obtained the adduct 97 as a 3:1 ratio of C-14β(H) and C-14α(H) epimers in nearly quantitative yield. It is interesting to note the marked differences in the approaches devised by both Valenta[3] and Grieco[30] despite the fact that both groups employed a Diels-Alder reaction to assemble the BC rings in route to the same natural product.

The sequence[30] continued with reduction from the convex face of the C-7 ketone in 93 to furnish the tetracyclic δ-lactone 94 having the correct relative stereochemistry at C-4, C-5, C-7, C-8, C-10, and C-14 for the quassinoids. Deprotection of the C-1 methyl ether in 94 following a procedure of Fujita,[34] reduction, and protection of the lactol, hydroboration-oxidation, and Collins' oxidation furnished the diketone 95 in a sequence that introduced two new chiral centers at C-13 and C-16. The stereochemistry of the latter center was presumably the result of acid-catalyzed equilibration of the intermediate lactol to favor (anomeric effect) an axially oriented C-16β methoxy group. The stereochemistry of the former center was not immediately apparent since the nature of the interlocking ring system in the diketone 95 demanded that either the B, C, or D ring exist in a boat conformation. As

shown in Scheme 19, it was possible for the C-13 methyl group

Scheme 19



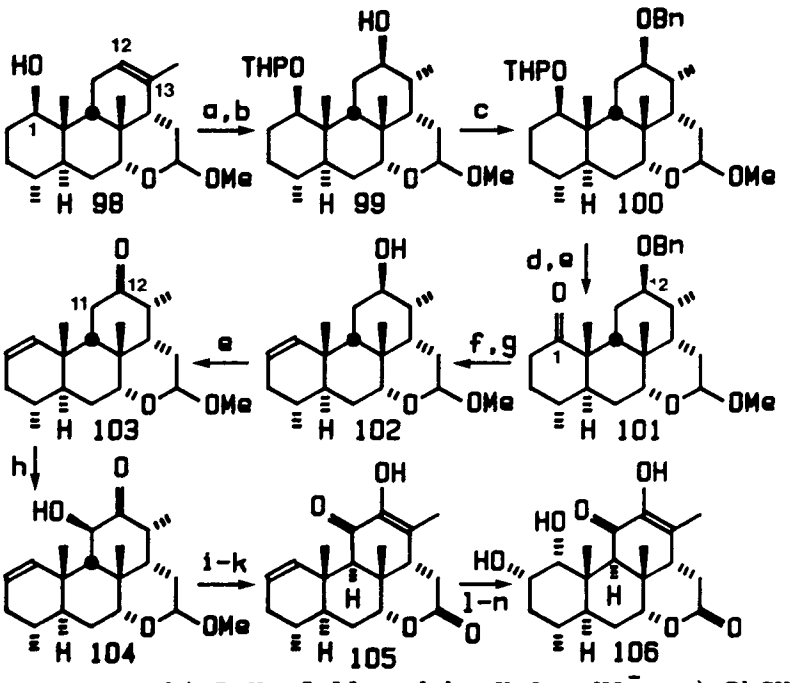
to adopt either the α-orientation where the C ring adopted a boat conformation as in 95a or the β-orientation where the D ring adopted a boat conformation as in 95b. In our own investigations, we noted that the $J_{13,14}$ coupling constant was consistent with a dihedral angle of ca. 60° in agreement with the C-13α methyl stereochemistry in 95a as suggested by Grieco. MM2 calculations also favored the C-13α methyl orientation with the C ring in a boat conformation.

The next phase of the synthesis focused on the correction of the C-9β(H) stereochemistry. Generation of the bis(enolate) of diketone 95 in Scheme 18 under kinetic conditions and oxygenation with Mimoun's reagent[10] led to the bis(α-ketol) 96 in 35% yield. The further oxidation[29b] of 96 using sodium methoxide in DMSO in the presence of a trace of oxygen and in the presence of methyl iodide led directly to the O-methyl ether of the bis(diosphenol). The oxidation of the α-ketol in the C ring of 96 to the O-methyl diosphenol permitted the

equilibration of the C-9β(H) center to the thermodynamically favored C-9α(H) configuration and thus addressed the last stereochemical problem in route to quassin (5). Hydrolysis of the protected lactol furnished neoquassin and oxidation with Fetizon's reagent[35] delivered quassin (5).

Drawing upon intermediates generated in this approach to quassin (5), Grieco also completed a synthesis of castelanolide[31] (106) and klaineanone[32] (46) from the olefin 98. In the castelanolide synthesis in Scheme 20, the initial trans-

Scheme 20



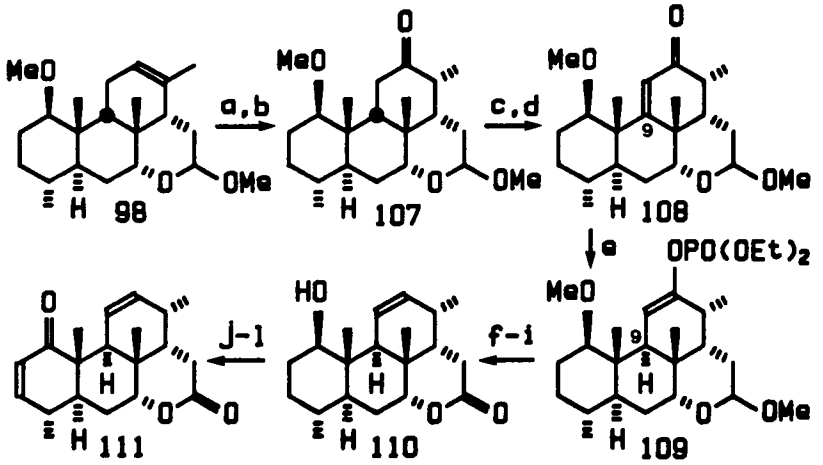
a) DHP, PPTS b) B_2H_6 followed by H_2O_2, HO^- c) $PhCH_2Br$, NaH, n-Bu_4NI d) MeOH, PPTS e) $CrO_3 \cdot 2Py$ (92%) f) LDA, $(Me_2N)_2POCl$ (77%) g) Li, $EtNH_2$, THF, t-BuOH (90%) h) LDA, MoOPH (45%) i) NaOMe, DMSO, MeOH (91%) j) 10% HCl, THF k) Ag_2CO_3 l) Ac_2O m) OsO_4, Py (98%) n) K_2CO_3, MeOH (91%)

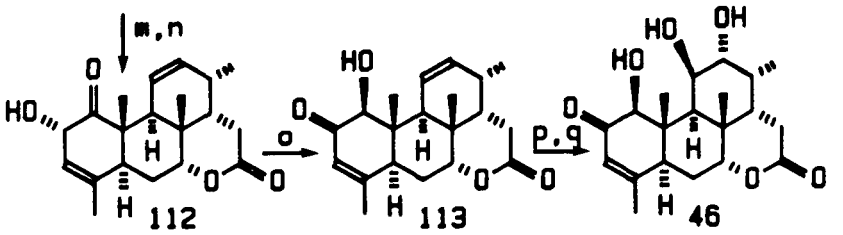
formations involved an interchange of the hydroxyl and olefin functionality in the A and C rings of 98 in order to reposi-

tion them in the C and A rings of 102, respectively. The C-1 hydroxyl group in hydroxy olefin 98 was first protected as the THP ether to permit hydroboration-oxidation of the C-12(13) olefin from the accessible β-face to secure the alcohol 99. Benzylation of the C-12β hydroxyl group, removal of the THP protecting group in 100, and oxidation furnished the ketone 101. Reduction of the C-1 enol phosphate[36] prepared from 101 as well as the C-12β benzyl ether gave the hydroxy olefin 102, and oxidation provided the keto olefin 103. The MoOPh oxidation[10] of the C-11(12) enolate of 103 and the sodium methoxide in DMSO oxidation[29b] of the α-ketol 104 again served to introduce the C ring diosphenol. Hydrolysis, oxidation of the δ-lactol and osmium tetraoxide oxidation of the A ring olefin finished the synthesis of castelanolide (106).

The klaineanone synthesis[32] represented the first successful synthesis of a quassinoid with the sensitive α'-hydroxyenone functionality[29e] in the A ring. As summarized in Scheme 21, the route was also noteworthy in that the lithium

Scheme 21





a) B_2H_6 followed by NaOH, H_2O_2 b) $CrO_3 \cdot 2Py$ c) LDA, TMSCl d) $Pd(OAc)_2$, Na_2CO_3 e) Li, NH_3, tBuOH followed by $(EtO)_2POCl$ f) Li, $EtNH_2$, tBuOH g) 5% HCl h) Jones' oxidation i) $BF_3 \cdot Et_2O$, $HSCH_2CH_2SH$ j) PCC k) HMDS, TMSI l) PhSeCl followed by H_2O_2 m) HMDS, Et_3N, TMSI n) MCPBA followed by n-Bu_4NF o) K_2CO_3, MeOH p) MCPBA q) 23% $HClO_4$

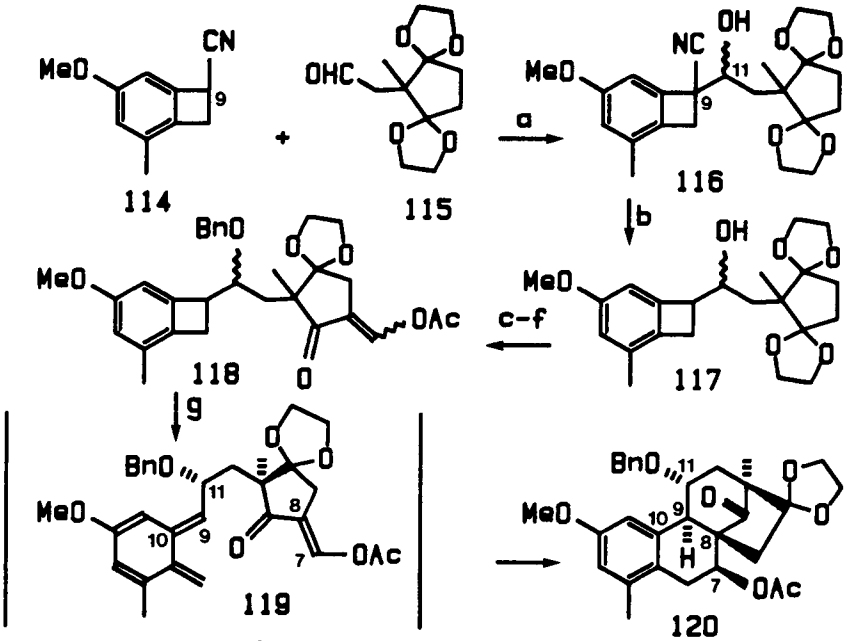
in ammonia reduction of the enone 108 and subsequent trapping of the enolate by diethyl phosphorochloridate led directly to the correct C-9α stereochemistry in contrast to other studies that led either to the incorrect stereochemistry or failed entirely. In order to introduce the α'-hydroxyenone functionality, the peracid oxidation of a trimethylsilyl dienol ether derived from the enone 111 led to the α-ketol 112. A base-catalyzed ketol tautomerization of 112 under carefully defined conditions secured the α'-hydroxyenone 113, and an epoxidation-hydrolysis introduced the trans-diol in the C ring of klaineanone (46).

(c) A-ABC...ABCD Approach

Although both the Valenta[3] and Grieco[30-32] approaches employed an intermolecular Diels-Alder reaction with considerable success, the intense interest in the intramolecular version[37] of this reaction was soon to attract attention as a viable alternative for the synthesis of quassinoids. Kametani[38] reported initial studies in 1980 directed toward

klaineanone (46) that were based upon the now familiar use of intramolecular Diels-Alder reaction of ortho-quinodimethanes. As shown in Scheme 22, the critical features of this approach

Scheme 22



a) $NaNH_2$, NH_3, -78° (66%) b) Na, NH_3 (60%) c) $PhCH_2X$ d, 10% HCl e) NaH, HCO_2Et f) Ac_2O g) o-$C_6H_4Cl_2$, 190° (41%)

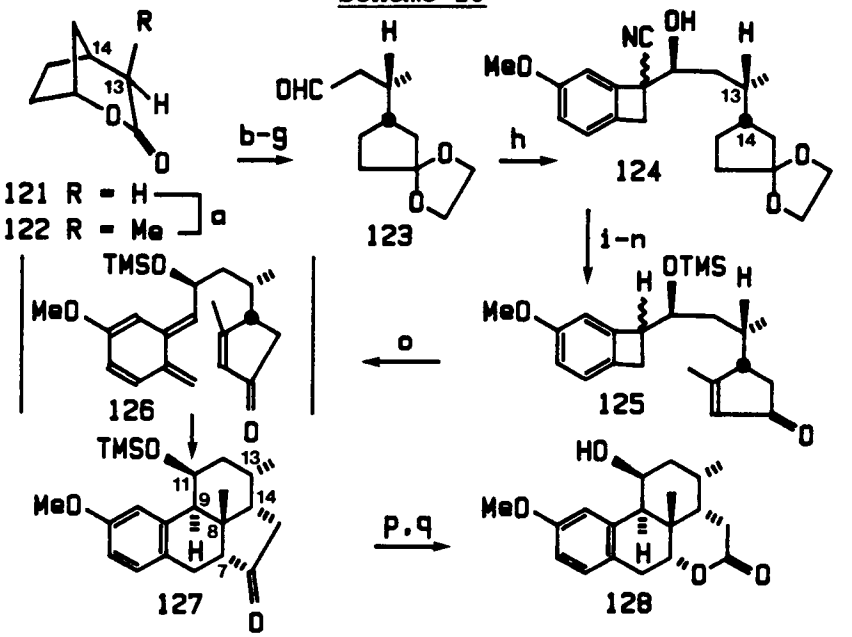
included the use of a benzocyclobutene that served as a masked equivalent of the required diene and an expendable cyano group on the cyclobutyl subunit that permitted the construction of the C-9,11 bond linking the dienophile and the diene precursor. The condensation of the cyano-substituted benzocyclobutene 114 with the aldehyde 115 secured the β-hydroxynitrile 116 that possessed progenitors of both the diene and dienophile. A straightforward sequence involving the reductive elimination of the cyano group gave 117, and the selective hydrolysis of one of the ketal protecting groups

furnished the β-acetoxyenone 118 as a mixture of diastereomers. The thermolysis of these benzocyclobutenes 118 generated an ortho-quinodimethane intermediate 119 that trapped the dienophilic β-acetoxyenone and delivered the tetracyclic ketone 120 having the relative sterochemistry at C-7, C-8, C-9, and C-11 displayed in Scheme 22. Assuming that the ring opening of the benzocyclobutene 118 generated the C-9,10 olefin bond with E-stereochemistry as shown in 119, it seemed fair to conclude, particularly based on the 41% yield of product 120, that the predominant diastereomer in 118 had the C-11(S) configuration. The relative stereochemistry at the remaining C-7, C-8 and C-9 positions in 120 arose from the exo-addition of the dienophilic component to the β-face of the diene assuming that the β-acetoxyenone had E-stereochemistry about the C-7,8 bond. We cannot determine whether the major diastereomer of 118 had the E-stereochemistry or E/Z-isomerization of 118 preceded the generation of 116. Although structural features in 120 related this intermediate to the quassinoids, the inversion of stereochemistry at C-7 and the introduction of the C-10β angular methyl group would require a number of additional transformations in order to reach klaineanone (46).

In a related approach[39] that appeared several years later, the problems encountered with the C-7 stereochemical issue were resolved by selecting a different dienophile. Rather than the β-acetoxyenone 118 having an exocyclic olefinic bond as in in Scheme 22, Kametani constructed a substituted 2-cyclopentenone 125 having an endocyclic olefinic bond as

shown in Scheme 23.

Scheme 23

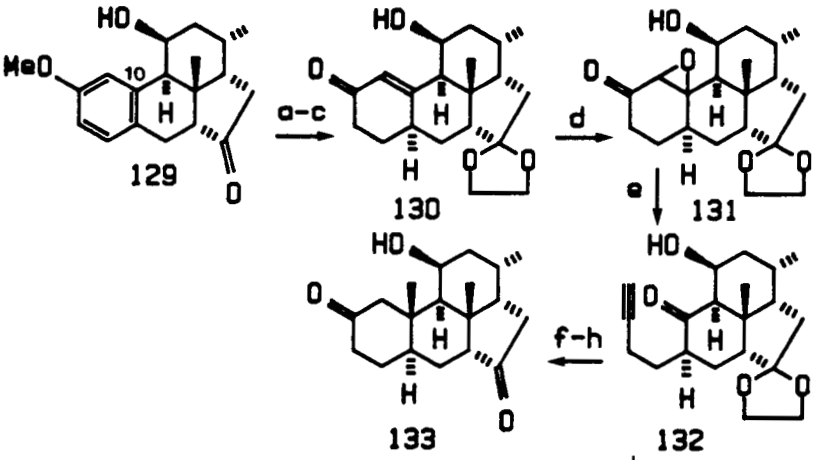


a) LDA, MeI b) $LiAlH_4$ c) TsCl d) Jones' oxidation e) EG, p-TsOH f) KCN g) i-Bu_2AlH h) $NaNH_2$, 4-methoxybicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile, -78° i) Na, NH_3 j) H_3O^+ k) LDA, TMSCl l) $Pd(OAc)_2$ m) Me_2CuLi followed by TMSCl n) $Pd(OAc)_2$, p-benzoquinone o) 210-230° p) H_3O^+ q) MCPBA

In addition, the correct relative stereochemistry of the C-13 and C-14 centers was addressed early in the synthesis through the stereoselective methylation of the lactone 121 derived from norcamphor. As in the preceding route, the exo-addition of the dienophile to the β-face of the ortho-quinodimethane led to the Diels-Alder adduct 127 having the correct relative stereochemistry at C-7, C-8, and C-9 as well as C-13 and C-14. Unlike the route presented in Scheme 22 in which the ultimate adduct had a C-11α hydroxyl group, the predominant stereoisomer in the condensation of 4-methoxybicyclo[4.2.0]octa-

1,3,5-triene-7-carbonitrile with the aldehyde 123 led to an adduct having the desired C-11β hydroxyl group. An X-ray structure of the C-8β desmethyl analog of 128, that was prepared by a similar sequence, secured these stereochemical assignments. As shown in Scheme 24, the further progres-

Scheme 24



a) EG, p-TsOH b) Li, NH_3, tBuOH c) PyH^+TsO^-, benzene, heat d) NaOH, H_2O_2, 60° (51%) e) $TsNHNH_2$, HOAc, -40° (72%) f) MeLi g) TFAA, TFA, 60° h) KOH

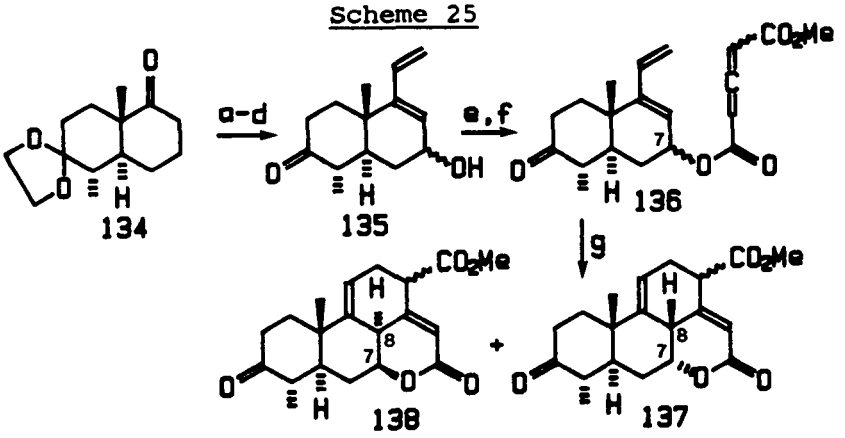
sion[39b] of the tetracyclic ketone 129 required the introduction of the C-10β angular methyl group, and following a procedure developed by Kametani[40] for a synthesis of hibaol, the Birch reduction of 127 and an Eschenmoser fragmentation[41] of the epoxyketone 131 delivered the acetylenic ketone 132. Addition of methyllithium and reclosure of the A ring furnished the tetracyclic diketone 133, an attractive precursor to various quassinoids.

(d) B-AB-ABCD Approach

Kanematsu[42] described another intramolecular Diels-Alder approach to the quassinoids in which an allene-1,3-dicarboxyl-

ate served as the dienophile in constructing a tricyclic ABCD intermediate from an AB ring diene. The bicyclic ketone 134 was elaborated to the vinylcyclohexene 135. Coupling with 4-carbomethoxy-3-chlorocrotonic acid and dehydrochlorination furnished the allene-1,3-dicarboxylate 136 as a mixture of C-7 epimers as shown in Scheme 25. The Diels-Alder reaction of

Scheme 25



a) PhSeCl, LDA followed by H_2O_2, Py b) LiC≡CH c) 25% H_2SO_4, 25° d) H_2, Pd-$BaSO_4$, quinoline e) DCC, $HO_2CCH=C(Cl)CH_2CO_2Me$ f) Et_3N g) o-xylene, 145°C

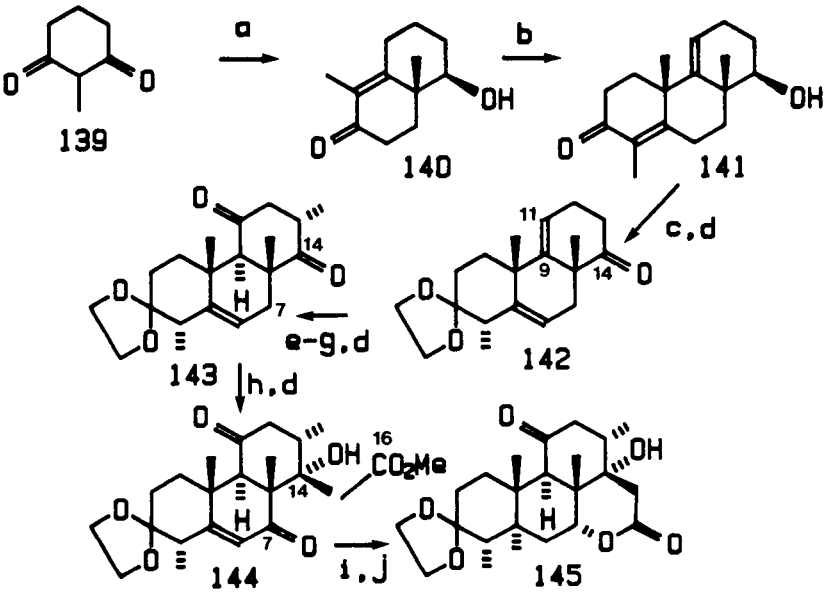
this mixture at 145°C produced a 1.7 to 1 mixture of the C-7β,8β(H) and C-7α,8α(H) adducts 137 and 138, respectively, in 46% yield. Unlike the Kametani approach,[38,39] the further progression of intermediates in this route will need to address the problem of introducing the C-8β angular methyl substituent.

(e) C-BC-ABC-ABCD Approach

The versatility of the Robinson annelation[43] for the assembly of polycyclic natural products led a number of groups to adopt this particular approach for the synthesis of quassinoids. In 1981, Takahashi[44] recorded a sequence in

which 2-methyl-1,3-cyclohexane-dione (139) served as a B ring progenitor leading to the tricyclic ketone 141 as the key intermediate in a process involving two successive Robinson annelations as shown in Scheme 26. The ketalization of 141

Scheme 26



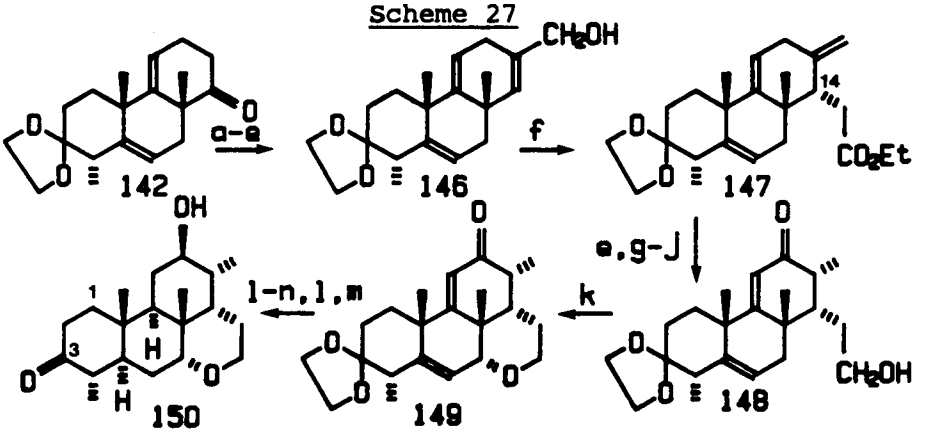
a) see reference 92 b) CH_2=CHCOEt c) EG, p-TsOH d) $CrO_3 \cdot 2Py$ e) LDA, MeI f) $LiAlH_4$ g) B_2H_6 followed by NaOH, H_2O_2 h) $LiCH_2CO_2Li$ followed by CH_2N_2 i) $NaBH_4$ j) Ag_2O or Jones' oxidation

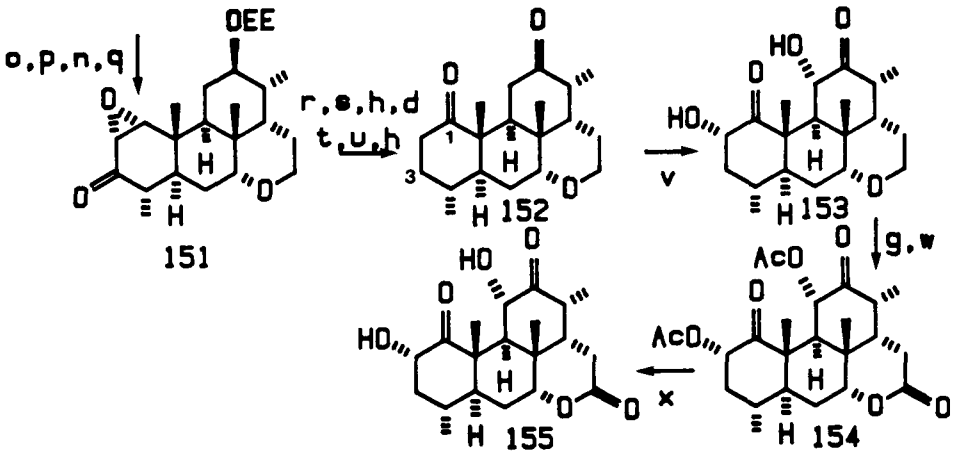
with ethylene glycol, Collins' oxidation, and methylation delivered the ketone 142 having all but the C-15 and C-16 carbons necessary for a synthesis of a tetracyclic quassinoid. Studies designed to introduce the remaining two-carbon acetate residue at C-14 were frustrated by the hindered nature of the C-14 ketone in 142 that resisted reaction with enolates or reaction with phosphonate Wittig reagents. The condensation of the Grignard reagent of 1-bromo-2-ethoxyacetylene with ketone 142 did, however, provide an adduct, but subsequent

efforts to manipulate the C-9(11) olefin in order to introduce a C-11 oxygen substituent were problematical. A successful resolution of this problem involved the selective hydroboration-oxidation of the C-9(11) olefin and a Collins' oxidation in order to obtain the diketone 143. A selective condensation of 143 at C-14 with the dianion of acetic acid and an allylic oxidation at C-7 introduced the remaining two carbons and set the stage for the closure of the D ring, but unfortunately, the stereochemistry of the carbomethoxymethyl group at the newly created C-14 center was epimeric with that required for the natural quassinoids. Reduction of both the C-7 ketone and the C-16 ester in 144 with sodium borohydride provided a δ-lactol, albeit only in 22% yield. A silver oxide or Jones' oxidation of this δ-lactol furnished the δ-lactone 145, as confirmed by an X-ray crystallographic determination. Efforts to effect the 1,2-transposition of the C-14 ketone to the C-13 position early in the sequence with a view to introducing the two-carbon fragment at C-14 by other means were, however, unsuccessful.

In another approach in Scheme 27 that ultimately led to a

Scheme 27





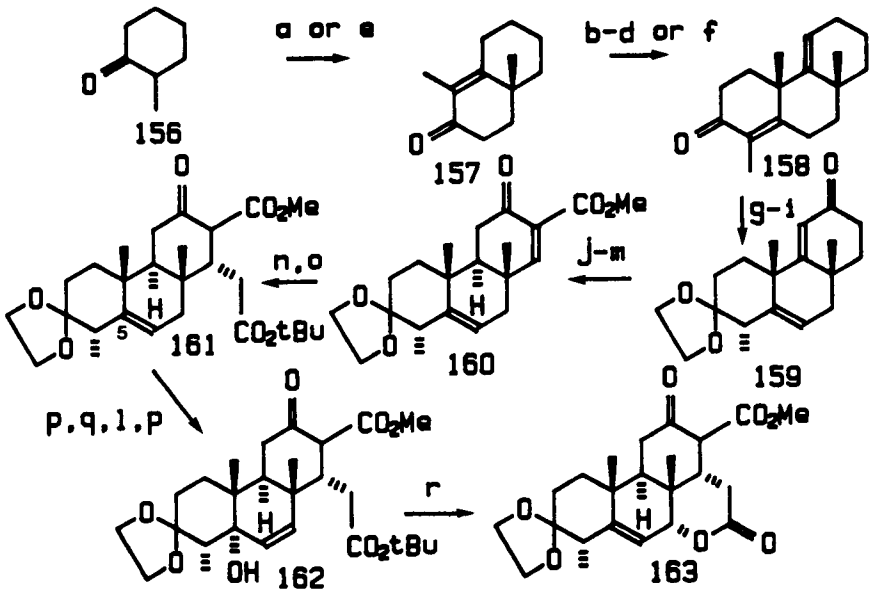
a) NaH, $EtOCO_2OEt$ b) $NaBH_4$ c) MsCl, Py d) DBU e) $LiAlH_4$ f) $CH_3C(OEt)_3$, heat (88%) g) Ac_2O, Py h) $CrO_3 \cdot 2Py$ i) H_2, PtO_2 j) KOH, MeOH k) $Pb(OAc)_4$, hv (52%) l) Li, NH_3 m) HCl, THF n) CH_2=CHOEt, PPTS o) PhSeCl p) MCPBA q) H_2O_2, NaOH r) $LiAlH(OtBu)_3$ s) p-TsCl t) p-TsOH, EtOAc u) H_2, Pd-C v) LDA, TMSCl followed by MCPBA and HCl, THF (37%) w) RuO_4, CCl_4 (24%) x) 3M H_2SO_4, THF

successful total synthesis of (±)-amarolide (155), Hirota and Takahashi[45] converted the tricyclic enone 142 to the allylic alcohol 146 and employed a Claisen rearrangement to introduce the two-carbon appendage at C-14 needed ultimately for the δ-lactone of amarolide. Subsequent critical transformations involved a photochemical closure of the alcohol 148 in the presence of lead tetraacetate in order to secure the tetrahydropyran 149, a lengthy sequence for the 1,3-transposition of the C-3 ketone in 150 to the C-1 position in 152, and the peracid oxidation of the bis(trimethylsilyl enol ether) of 152 to obtain the bis(α-ketol) 153. A ruthenium tetraoxide oxidation of the tetrahydropyran ring delivered (±)-amarolide (155). Since amarolide had previously been converted to quassin,[46] this synthesis also constituted a formal synthesis of this

quassinoid as well.

In 1984, Heathcock[47] also reported a Robinson-based approach in Scheme 28 in which the stereocontrolled introduc-

Scheme 28



a) see reference 93 b) NaH, DMSO, $BrCH_2CH=C(Cl)C_2H_5$ c) $Hg(OAc)_2$, $BF_3 \cdot Et_2O$, HOAc d) KOH, aq. MeOH (61% overall) e) $ClCH_2CH_2COC_2H_5$, 2-naphthalenesulfonic acid (64%) f) $ClCH_2CH_2COC_2H_5$, NaH, DMSO followed by KOH, MeOH, heat (65%) g) CrO_3, Ac_2O, HOAc h) EG, 2-naphthalenesulfonic acid i) SiO_2, H_2O, CH_2Cl_2 j) Li, NH_3, t-BuOH k) Stiles' reagent l) CH_2N_2 m) PhSeCl followed by H_2O_2 n) $H_2C=C(Ot\text{-}Bu)OTBS$, CH_3CN, 15kbar o) KF, aq. THF p) MCPBA q) PhSeNa, EtOH r) PCC, CH_2Cl_2 (55%)

tion of the lactone D ring was achieved in an ingenious manner. The repetitive annelation of 2-methylcyclohexanone (156) with ethyl vinyl ketone (or its equivalent) furnished the tricyclic enone 158. Unlike the Takahashi synthesis[44] in Scheme 26, Heathcock employed a Birch reduction to introduce the trans-fusion of the BC rings and, in addition, pursued

those quassinoids having the C-13 carbomethoxy group rather than the C-13 methyl group. The intention was presumably to introduce a C-13 ester and subsequently to effect a remote functionalization of the C-8β methyl group in order to prepare the pentacyclic quassinoids. However, since this latter reaction was not achieved in this study, we have included the discussion of this route here. The addition[48] of the tert-butyldimethylsilyl ketene acetal of tert-butyl acetate to enone 160 under high pressure afforded the Michael adduct 161 stereoselectively and in high yield. Conversion of the C-5 olefin in 161 to the allylic alcohol in 162 employed the Sharpless procedure,[49] and a remarkable solvolytic cyclization of 162 in the presence of pyridinium chlorochromate, but not other more traditional solvolytic procedures, produced the tetracyclic lactone 163.

2. Pentacyclic Skeleton

As in the previous discussion, many of the approaches to the pentacyclic quassinoids involve familiar themes in which the Diels-Alder and Robinson annelations orchestrate the ring assembly processes. With a few exceptions,[7] most investigations in this series have again focused on the picrasane-type intermediates with either an 8,13-oxymethylene or 8,11-oxymethylene bridge found, for example, in quassimarin (8) or bruceolide (9) in Scheme 1.

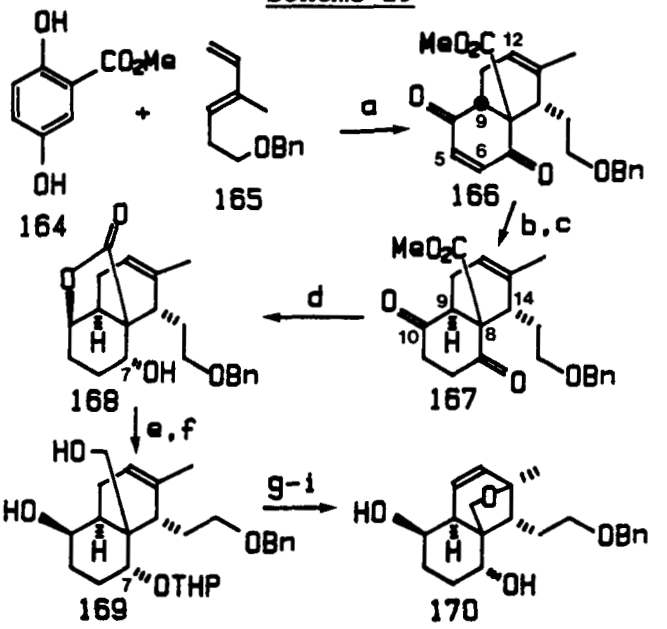
(a) B-BC-BCE-BCDE...ABCDE Approach

Both Kraus[51] and Stevens[52] envisioned a convergent scheme

for the synthesis of the quassinoids that utilized a Diels-Alder reaction of a substituted para-benzoquinone to prepare a bicyclic BC intermediate carrying functionality suitable for introducing the remaining rings. Weller[53] adopted a similar approach in which an ortho-benzoquinone would serve as the B ring dienophile. In this sense, these routes have their lineage in the synthetic route originally undertaken by Valenta,[3] although they differ in employing benzoquinone dienophiles as progenitors of the B and not the C ring.

As shown in Scheme 29, Kraus[51] employed the Diels-Alder

Scheme 29



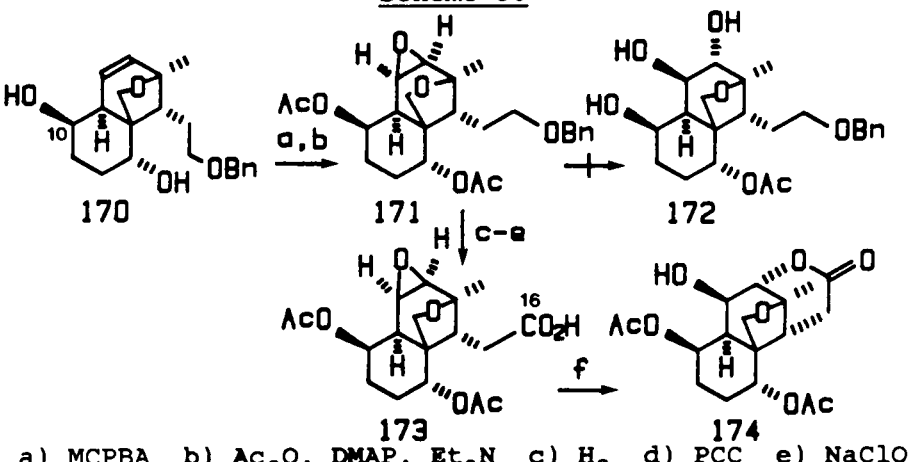
a) Ag_2O b) Zn, HOAc c) Al_2O_3 d) $LiB[CH(Me)Et]_3H$ e) DHP, PPTS f) $LiAlH_4$ g) H_3O^+ h) PhSeCl i) H_2O_2

reaction of an unstable quinone 164 and the diene 165 to afford the cis-fused enedione 166. Reduction of the less hindered C-5 olefin in 166 and the epimerization of the C-9 position provided the trans-fused diketone 167 having the

stereochemistry characteristic of the C-8, C-9, and C-14 positions of the quassinoids. The stereoselective reduction of the diketone 167 to the diaxial diol led to concomitant lactonization of the C-10β hydroxyl group with the C-8 ester thereby differentiating between these axial hydroxyl groups and providing the lactone 168. This intriguing reaction facilitated the protection of the C-7α hydroxyl group as the tetrahydropyranyl (THP) ether, and after further reduction of the lactone, permitted application of the Nicolaou[54] seleno-cyclization procedure to deliver the tricyclic diol 170 possessing the characteristic oxymethylene bridge of the pentacyclic quassinoids. As we shall make clear later in this discussion, this approach for introducing the E ring was subsequently taken up by a variety of other research groups.

Kraus' work[51] also highlighted the problems inherent in the introduction of the 11β,12α-diol functionality of the C ring. Failure to effect the trans-diaxial opening of the epoxide 171 to 172 in Scheme 30 using external nucleophiles

Scheme 30

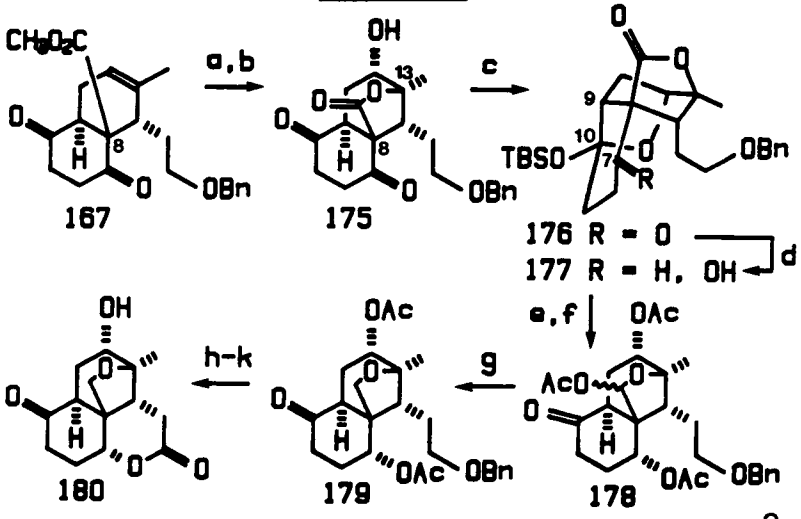


a) MCPBA b) Ac_2O, DMAP, Et_3N c) H_2 d) PCC e) $NaClO_2$, 2-methyl-2-butene f) CF_3CO_2H

led to the successful use of an internal nucleophile, a C-16 carboxylate, in order to open the epoxide 173 and obtain lactone 174. Although saponification of the lactone 174 should furnish the trans-diaxial diol 172, this operation was never actually reduced to practice, and other problems with the oxidation of the homoallylic C-10β hydroxyl group in 170 led to the development of an alternate route.

As shown in Scheme 31, this new route[51] capitalized on

Scheme 31



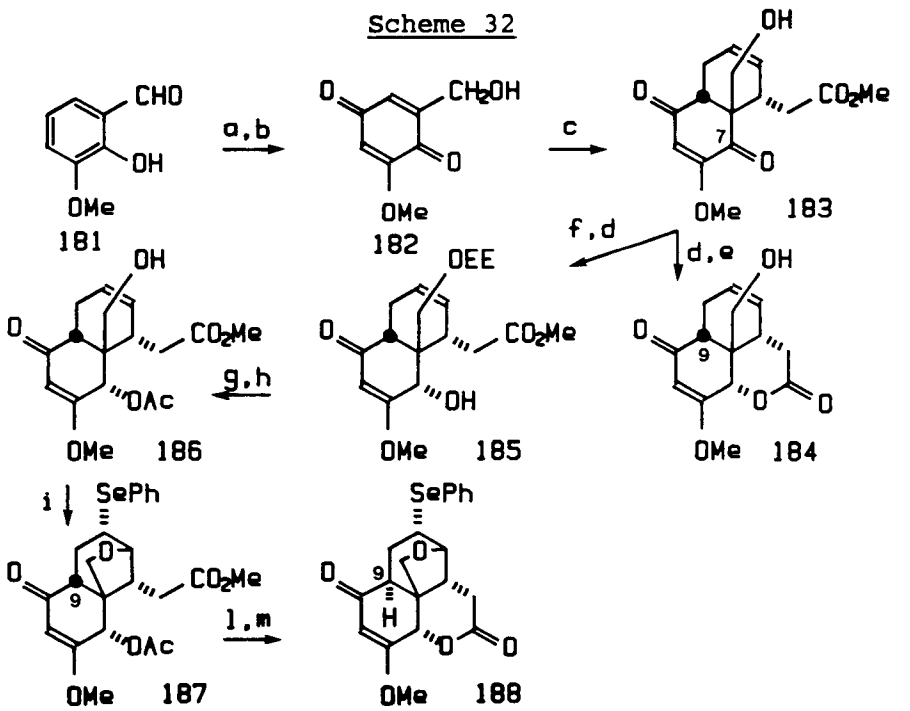
a) MCPBA b) $HClO_4$ c) t-$BuMe_2SiCl$, imidazole, 50° d) iBu_2AlH e) n-Bu_4NF f) Ac_2O g) Et_3SiH, $BF_3 \cdot Et_2O$ h) H_2, Pd/C i) Jones' oxidation j) K_2CO_3, MeOH k) 1M HCl

the same bicyclic diketone 167 that had been developed for the previous route but employed the C-8 carboxy group to establish a lactone bridge to the C-13 position rather than the C-10β hydroxyl group as in Scheme 29. The epoxidation of diketone 167 and acid-catalyzed lactonization furnished the tricyclic diketone 175. Efforts to protect the C-12α hydroxyl group as the TBS ether led unexpectedly to epimerization at C-9 and formation of the curious TBS-protected hemiketal 176. This

ketalization was turned to an advantage in differentiating between the C-7 and C-10 keto groups. Stereoselective reduction of the C-7 ketone and the lactone in 176 led ultimately to the tricylic ketone 179. The subsequent deprotection of the benzyl ether and oxidation led to the δ-lactone 180 having the BCDE rings in place and suitable functionality for the elaboration of the remaining A ring.

In 1985, Stevens[52a] reported a route that paralleled Krause's[51] approach in the sense that both routes employed a para-benzoquinone dienophile as a B ring progenitor. As shown in Scheme 32, the Diels-Alder reaction of the para-benzoquin-

Scheme 32



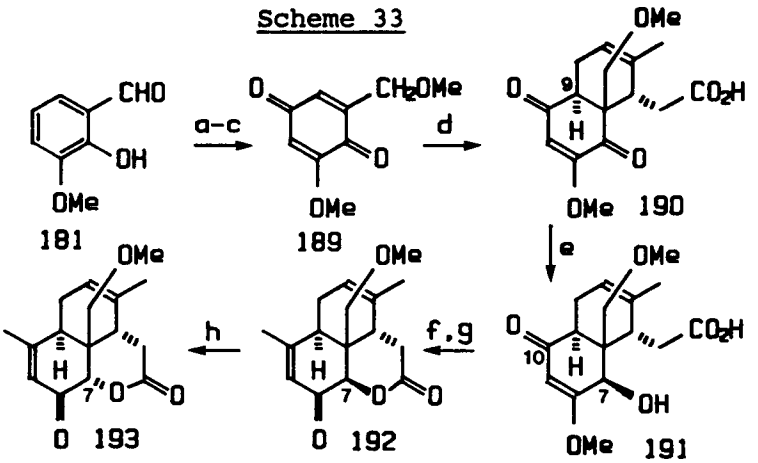
a) H_2, Ra(Ni) b) salcomine, O_2 c) methyl 3,5-hexadienoate d) $NaBH_4$ e) $NaHCO_3$ f) $CH_2{=}CHOC_2H_5$ g) Ac_2O h) H_3O^+ i) PhSeCl j) NaOH k) p-TsOH, benzene

one 182 and methyl 3,5-hexadienoate delivered the cis-fused BC diketone 183. The regio- and stereoselective reduction of the

C-7 keto group afforded the tricyclic BCD lactone 184, but as in Weller's case,[53] Stevens was unable to effect the epimerization of the C-9β(H) stereochemistry in 184; however, Stevens achieved this epimerization in a tricyclic BCE intermediate 187 that possessed a bridging tetrahydrofuran ring and that was prepared after some functional group acrobatics. Saponification and lactonization of 187 proceeded with concomitant epimerization at C-9 to afford the tetracyclic lactone 188.

In a subsequent study shown in Scheme 33, Stevens[52b] was

Scheme 33



a) $NaBH_4$ b) NaH, MeI c) salcomine, O_2 d) CH_2=CHC(CH_3)=$CHCH_2CO_2H$, benzene, 80°C or CH_2Cl_2, 25°C followed by $NaHCO_3$ e) $NaBH_4$, -30°C f) MeLi, THF, -40°C g) Ac_2O h) DBU

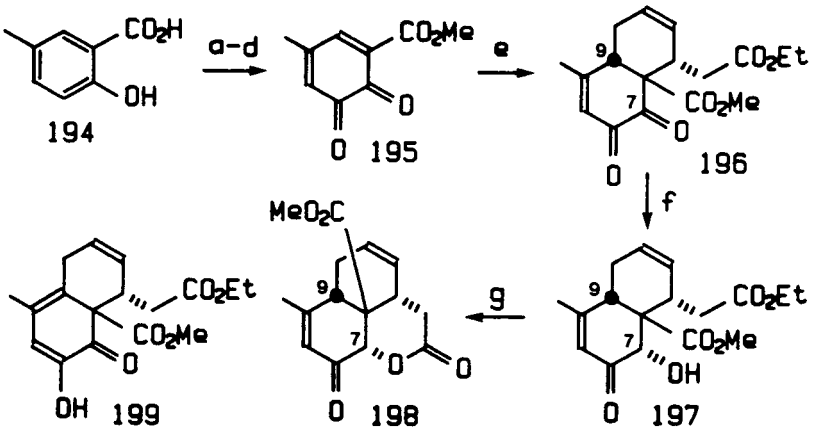
able to epimerize the C-9β(H) stereochemistry in the initial Diels-Alder adduct in order to obtain the trans-fused diketone 190. In contrast to the low-temperature, sodium borohydride reduction of the cis-fused adduct 183 in Scheme 32 that produced the desired C-7α hydroxyl stereochemistry, the reduction of 190 in Scheme 33 delivered the undesired C-7β alcohol. However, an efficient solution to this stereochemical imper-

fection was found in the context of introducing the C-19 methyl group. The addition of methyllithium to the C-10 ketone in 191 and dehydration of the hydroxy acid provided the tricyclic δ-lactone 192 still having the incorrect C-7 stereochemistry. Since the nature of the ring fusions in 192 dictated that at least one of the rings must adopt a boat conformation, base-catalyzed epimerization of the C-7 position in 192 favored the δ-lactone 193 with the C-7β(H) stereochemistry and all three rings in chair conformations.

(b) B-BC-BCD...ABCDE Approach

In a slightly different tack, Weller[53] investigated an ortho-benzoquinone dienophile as a progenitor of the B ring. Anticipating that the 3,5-substituted ortho-benzoquinone 195 in Scheme 34 would react regioselectively at the C-3(4)

Scheme 34



a) Br_2, HOAc b) NaOH, H_2O, $CuSO_4$, heat c) $BF_3 \cdot Et_2O$, MeOH d) Ag_2O e) ethyl 3,5-hexadienoate (80%) f) $NaBH_4$, EtOH, THF (25%) g) TFA (74%).

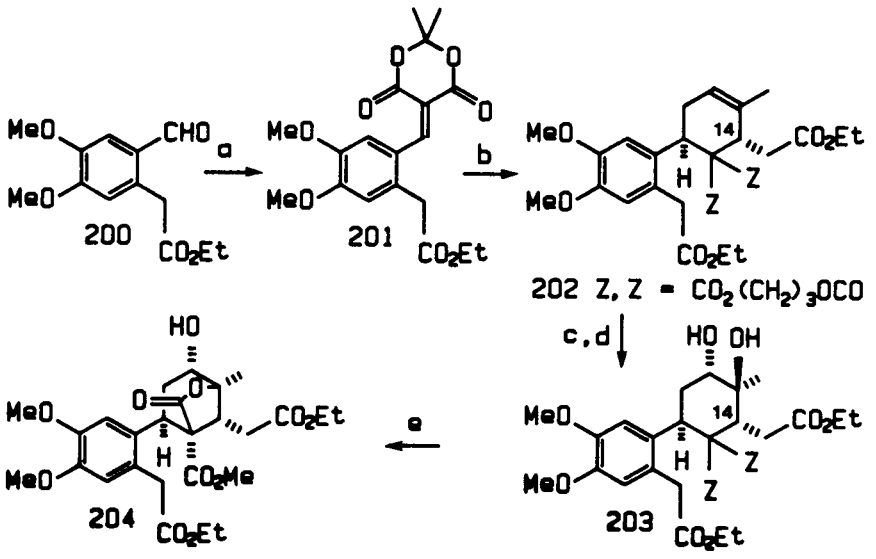
position based on the work of Ansell,[55] Weller found that the

Diels-Alder reaction of 195 and ethyl 3,5-hexadienoate gave the adduct 196. The efficient construction of this attractive intermediate was followed by efforts to introduce the D ring, and success in this instance depended upon the regio- and stereoselective reduction of the C-7 ketone, a reaction that led ultimately to a modest yield of α-ketol 197. Lactonization led to the tricyclic BCD intermediate 198, and additional studies revolved around the epimerization of the C-9β(H) stereochemistry in either 196, 197, or 198. In the latter two cases, undesired epimerization occurred at the C-7 position, and in the case of 196, base-catalyzed treatment led to the diosphenol 199.

(c) A-AC-ACE....ABCDE Approach

In a subsequent study, Kraus[56] sought to address the problem of introducing the A ring earlier in the synthetic plan than that described in Scheme 29. As shown in Scheme 35,

Scheme 35



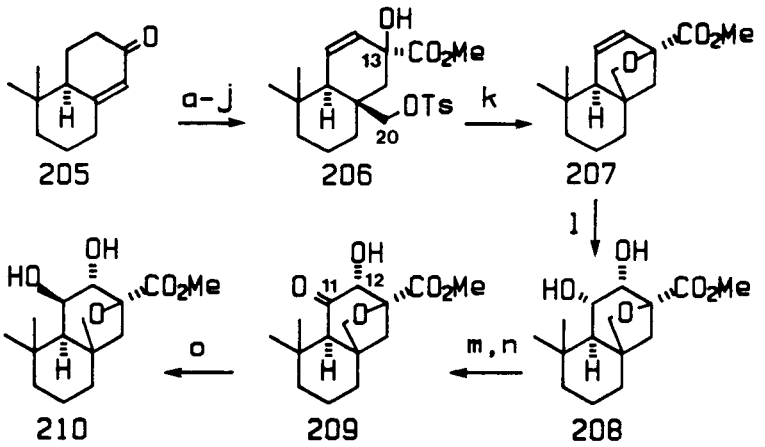
a) piperidine, HOAc, Meldrum's acid (92%) b) 110° (84% of C-14 mixture) c) MCPBA d) $HClO_4$, aq. THF e) CH_2N_2

the Diels-Alder reaction of the alkylidenemalonate dienophile 201 and a deconjugated sorbate diene furnished a 5:2 mixture of the desired C-14β(H) adduct 202 and the undesired C-14α(H) epimer. Epoxidation of the olefin in 202 and acid-catalyzed hydrolysis of the epoxide proceeded with concomitant saponification of the 1,3-dioxane-4,6-dione to produce the lactone 204 that potentially represented the ACE rings of a quassinoid. Unfortunately, efforts to implement a Dieckman condensation using the diester 204 in order to introduce the B ring were unproductive.

(d) C-BC-ABC-ABCD...ABCDE Approach

Fuchs[57] tackled the problem of introducing a trans-diaxial 11,12-diol of bruceantin (25) in the context of a model study for the BCE rings. As shown in Scheme 36, this

Scheme 36

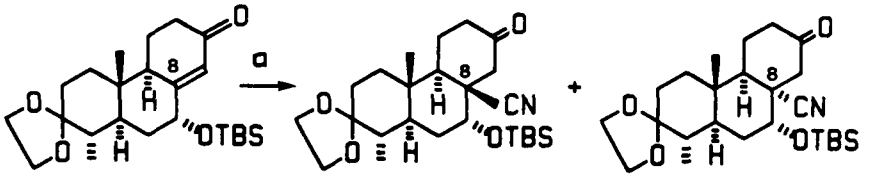


a) Et_3Al, HCN b) EG, p-TsOH c) $[C_6H_5NH]Br_3$ d) DBU, 150°C e) $LiAlH_4$ f) $NaBH_4$ g) n-BuLi, THF followed by TsCl h) $HClO_4$ i) $LiC(SMe)_3$ j) $HgCl_2$, HgO k) HMPA,

$120^{o}C$ 1) OsO_4 m) DMSO, TFAA n) Et_3N o) $NaBH_3CN$ sequence began with the Nagata hydrocyanation of the bicyclic enone 205 and introduction of the C-13 carbomethoxy group using tris(thiomethoxy)methyllithium. The closure of the tetrahydrofuran E ring involved nucleophilic attack by the C-13β hydroxyl group in 206 on the C-20 tosylate. Further elaboration of the olefin 207 to the 11β,12α-diol via an intermediate 11α,12α-epoxide was unsuccessful, and an alternate sequence involving the oxidation of the cis-diol 208 to the α-ketol 209 and the selective reduction of 209 with sodium cyanoborohydride furnished the trans-diol 210. It was of interest that neither epimerization at C-12 in the intermediate α-ketol 209 nor equilibration with the isomeric 12-keto-11-ol was observed.

Efforts[58a] to extend this model study to a tricyclic enone 211 in Scheme 37 encountered a lack of stereoselectivity

Scheme 37



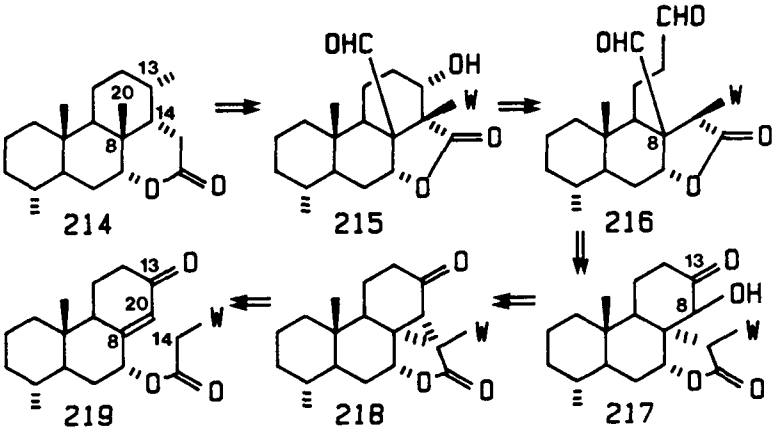
211 212 213

a) Et_2AlCN

in the C-8β hydrocyanation, and this disappointment prevented the extension of this approach to the preparation of an ABCE intermediate. In response to this difficulty, Fuchs[58a] developed a new, quite fascinating approach to an ABCD intermediate in which the functionalized C-8β methyl substituent was excised from the C ring of an intermediate enone 219 as shown

in an abbreviated retroanalysis in Scheme 38. The numbers

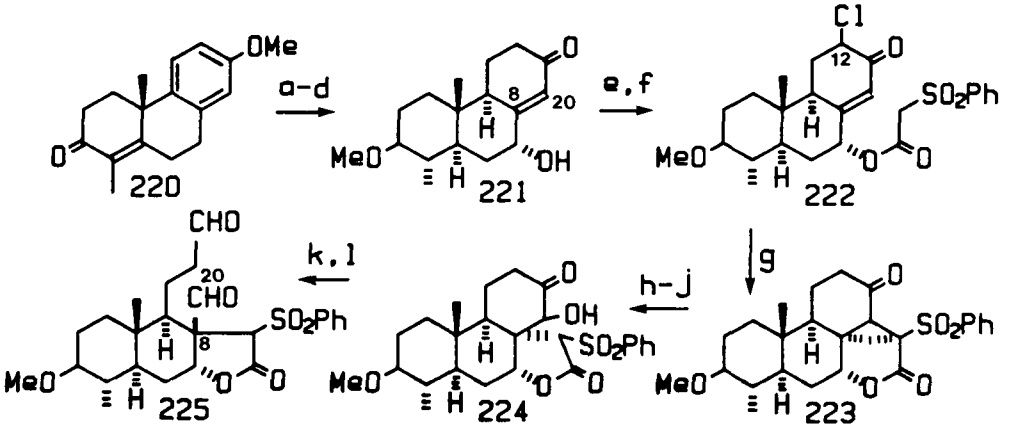
Scheme 38

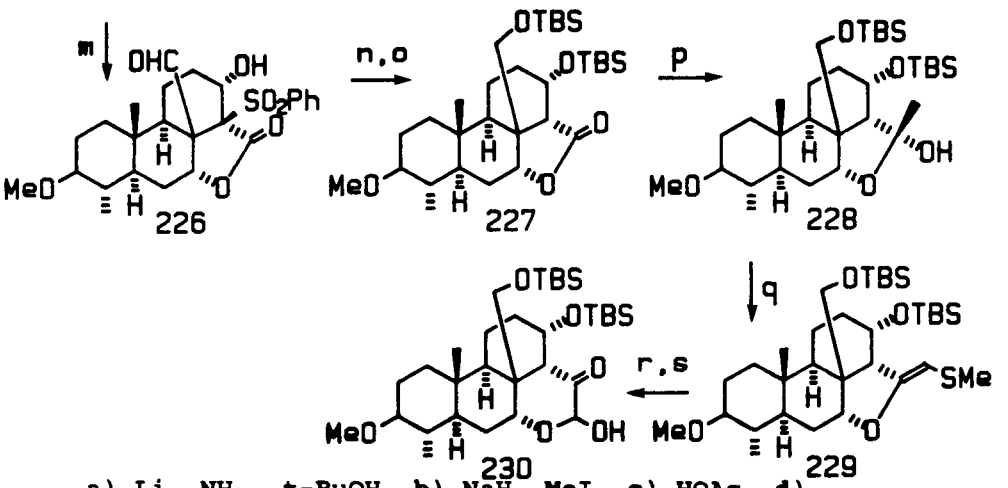


that appear in the structures 217, 218, and 219 delineate the pattern of bond forming reactions and excisions necessary, in a synthetic sense, to transform the tricylic enone 219 to the picrasane skeleton 214.

Following the precedent set by Graf,[2] Fuchs[58a] prepared the hydroxyenone 221 and after chlorination at C-12, introduced the α-(phenylsulfonyl)ester at the C-7α position as shown in Scheme 39. The cesium fluoride-mediated addition of the

Scheme 39





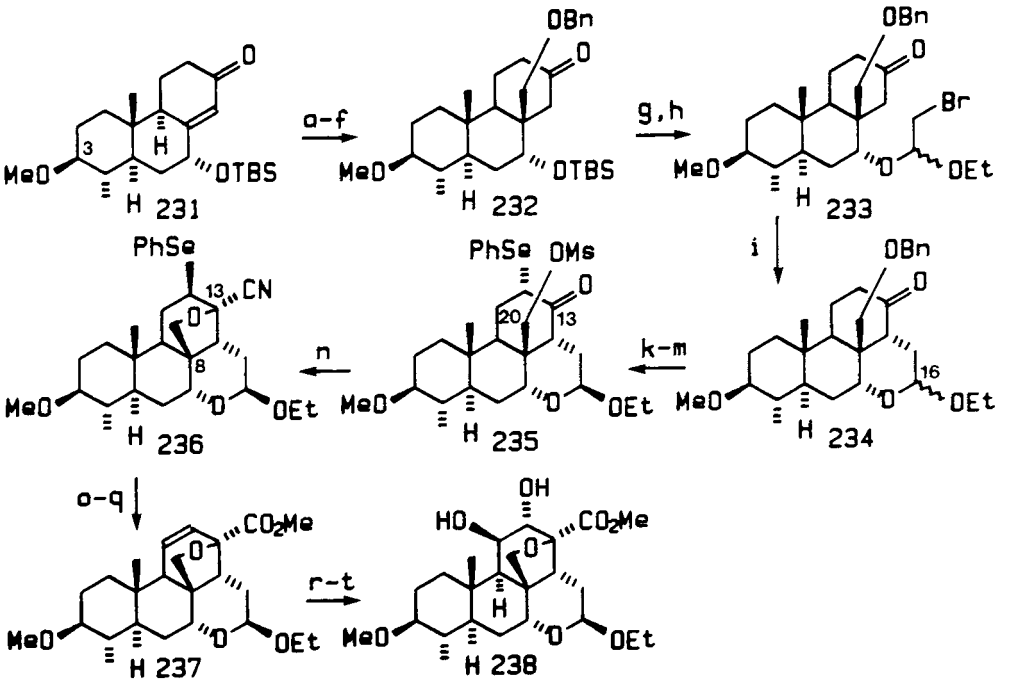
a) Li, NH_3, t-BuOH b) NaH, MeI c) HOAc d) $2KHSO_5 \cdot K_2SO_4 \cdot KHSO_4$, aq. THF (94%) e) NCS, LDA f) DCC, $PhSO_2CH_2CO_2H$ g) CsF h) $LiCuMe_2$ i) TMSCl j) O_3 k) $LiBH_4$ l) $NaIO_4$ m) Et_3N n) Al(Hg) (71%) o) $t\text{-}BuMe_2SiOSO_2CF_3$ p) MeLi q) DMSO, TFAA r) Et_3N s) OsO_4

anion of the α-(phenylsulfonyl)ester 222 to the α-face of the enone gave the pentacyclic cyclopropyl sulfone 223. Reductive cleavage of the cyclopropyl ring, trapping of the intermediate enolate with trimethylsilyl chloride, and ozonolysis of the trimethylsilyl enol ether delivered the α-ketol 224. The periodate cleavage of the diol derived from 224 revealed the C-8β aldehyde group that had begun its journey to this position as part of the enone functionality in 221. An intramolecular aldol reaction of 225 reformed the C ring in 226, and a standard sequence furnished the tetracyclic lactone 227. An interesting conversion of the hemiketal 228 to the β-(thiomethoxy)enol ether 229 set the stage for the oxidative ring expansion of 229 to the β-(oxo)hemiacetal 230, an ABCD intermediate lacking only the C-13 methyl of the quassinoid skeleton but possessing functionality suitable for elaboration

to a natural quassinoid.

The difficulties encountered with the stereoselective addition of cyanide to the enone 211 in Scheme 37 were surmounted in a subsequent study[58b] in which the C-3 ketal was replaced with a C-3β methoxy group. As shown in Scheme 40,

Scheme 40

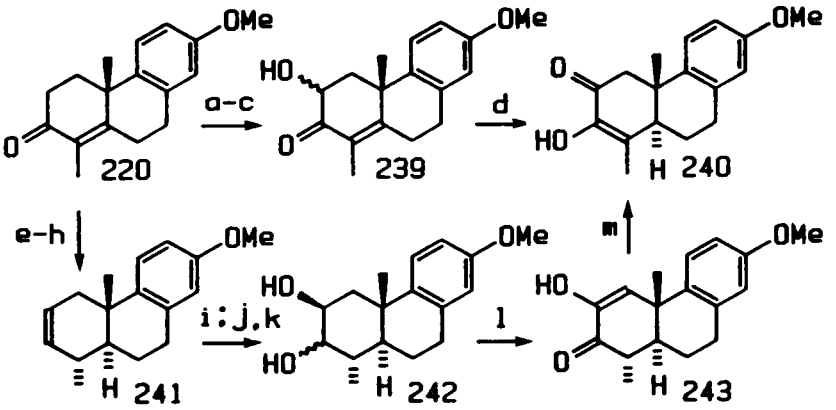


a) $AlEt_3$, HCN b) LDA, TMSCl c) DIBAL followed by HOAc d) i-Bu_2AlH e) BnBr f) H_3O^+ g) n-Bu_4NF h) $PhNMe_2$, $BrCH_2CH(OEt)Br$ i) t-BuOK, benzene j) TBSOTf, Et_3N, 0°C k) Li, NH_3 l) MsCl, Et_3N m) PhSeCl, THF, 0°C n) KCN, 18-crown-6 o) H_2O_2 p) HO^-, H_2O_2 followed by KOH q) CH_3I r) OsO_4 s) Swern oxidation t) n-Bu_4NBH_4

preparation of the bromacetal 233 using a straightforward series of reactions set the stage for the intramolecular alkylation that furnished the keto acetal 234 as a mixture of C-16 diastereomers. The conversion of one of these diastereomers to the α-(phenylselenyl)ketone 235 provided functionality

for the subsequent introduction of the trans-diol group. The addition of a cyanide nucleophile to the C-13 carbonyl generated a cyanohydrin with an axial hydroxyl group, and this intermediate, in turn, displaced the C-20 mesylate to provide the pentacyclic nitrile 236 having the desired C-8,13 oxymethylene bridge. Oxidative elimination of the phenylselenide and osmium tetraoxide oxidation of the olefin in 237 led to a cis-diol. The application of methodology for the conversion of a cis-diol to a trans-diol shown in Scheme 36 furnished the advanced intermediate 238. In model studies[18] designed to introduce the diosphenol functionality characteristic of the A ring of certain quassinoids as shown in Scheme 41, the Swern

Scheme 41



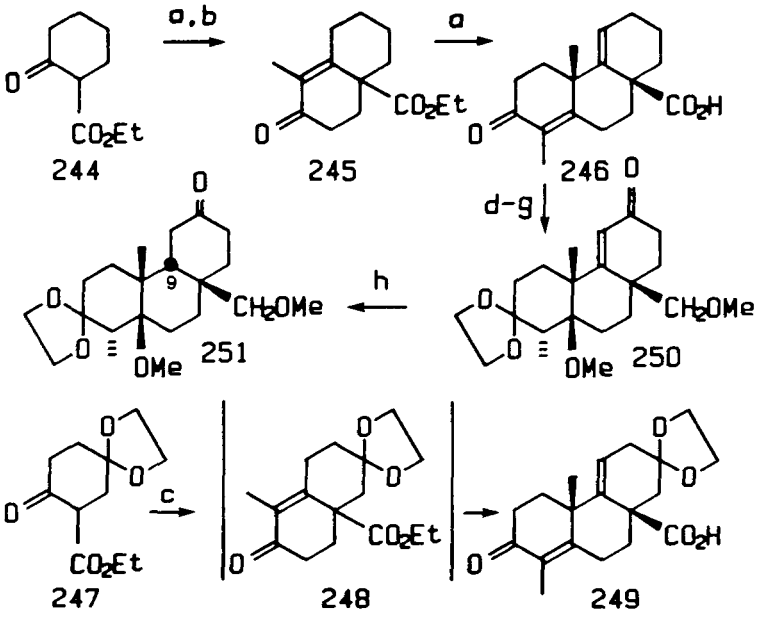
a) LDA, TMSCl, -78°C b) MCPBA c) 10% HCl d) KOMe (45%) e) $LiAlH_4$, $AlCl_3$ f) MsCl, Py g) NaSePh h) H_2O_2 i) OsO_4 j) MCPBA k) 7% $HClO_4$ l) Swern m) NaOMe, MeOH

oxidation of the diol 242 was preferable to the base-catalyzed isomerization of the α'-hydroxyenone 239 in order to obtain the diosphenol 240 characteristic of quassinoids such as bruceantin (25).

Based on the precedent described by Dutta,[59] we[60] exam-

ined two successive Robinson annelation of ethyl vinyl ketone to 2-carboethoxycyclohexanone in order to assemble the tricyclic enone 246 in Scheme 42. Although this enone served

Scheme 42



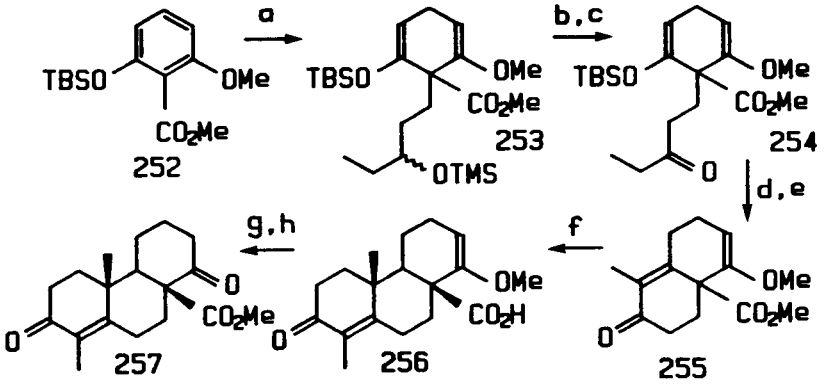
a) NaOEt, CH_2=$CHCOC_2H_5$ b) H_2SO_4, EtOH c) NaOMe, MeOH, CH_2=$CHCOC_2H_5$ or $ClCH_2CH_2COC_2H_5$, reflux d) EG, p-TsOH e) $LiAlH_4$ f) KH, MeI, 18-crown-6 g) CrO_3·2Py h) Li, NH_3, tBuOH

as the starting material for a synthesis of ferruginol and hinokione,[60b] we also planned to employ it in an approach to the quassinoids. Fuchs[58c] employed exactly Dutta's approach[59] in preparing the related tricyclic enone 249 in Scheme 42, and Grieco[29f] manipulated the acid 246 to secure the enone 250 but the lithium in ammonia reduction of 250 gave a tricyclic intermediate 251 with the undesired C-9β stereochemistry.

The annelation procedure developed by us had led to a tricyclic ABC intermediate that lacked functionality at the C-13 and C-14 positions. Mander[61] provided a solution to this

problem by devising an approach to a functionalized Wieland-Miescher ketone shown in Scheme 43. The reductive alkylation

Scheme 43

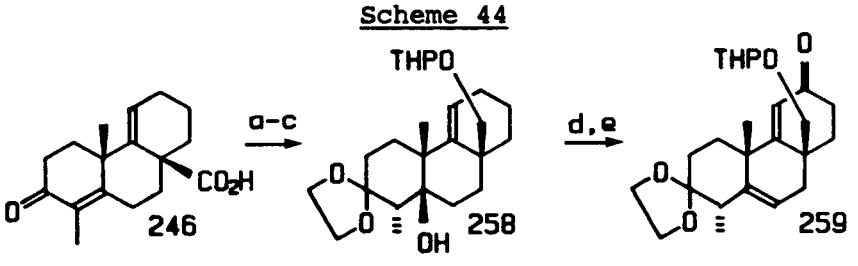


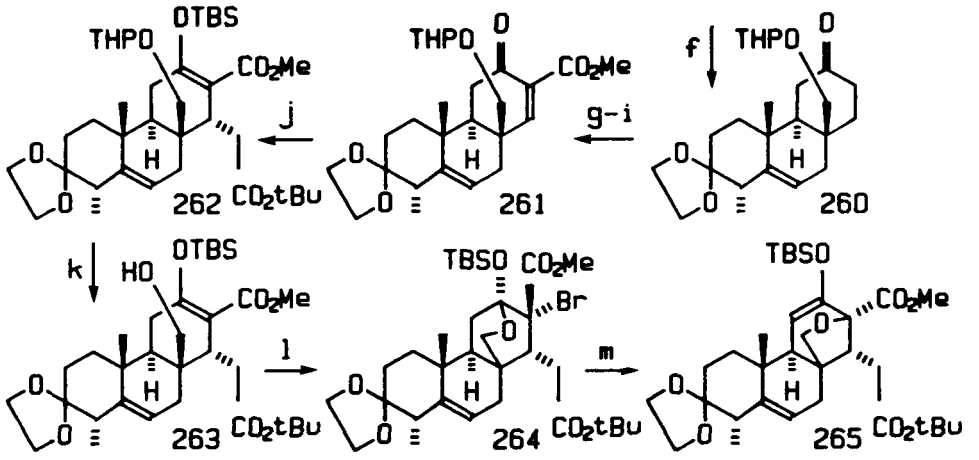
a) K, NH_3, -78°, KBr, $C_2H_5CH(OTMS)CH_2CH_2I$ (88%) b) aq. HOAc c) DMSO, DCC d) n-Bu_4NF e) K_2CO_3, CH_3OH f) $NaOCH_3$, $C_2H_5COCH_2CH_2Cl$ g) CH_2N_2 h) $Hg(NO_3)_2$, aq. CH_3CN

of the benzoate ester 252 with 3-(trimethylsilyloxy)-1-iodo-pentane provided the 1,4-cyclohexadiene 253. Subsequent deprotection, oxidation, and aldol condensation-dehydration steps provided the ketone 255, and an additional Robinson annelation furnished the intermediate 256. Hendrickson[62] reported the construction of a C ring precursor to the tetracyclic quassinoids that also relied on a Birch reduction.

Heathcock[63] reported the most successful work along lines that employed a Robinson annelation strategy. As shown in Scheme 44, the tricyclic acid 246 afforded the enone 259,

Scheme 44





a) EG, p-TsOH b) $LiAlH_4$ c) DHP, PPTS d) CrO_3, 3,5-dimethylpyrazole (71%) e) Ac_2O, DMAP, Py, reflux (63%) f) Li, NH_3 g) $MeOMgOCO_2Me$, DMF, reflux h) CH_2N_2 i) $SOCl_2$, syn-collidine (64%) j) CH_2=C(Ot-Bu)(OTBS), 7kbar, 5 d (81%) k) PPTS, EtOH (44%) l) NBS (84%) m) DMF, reflux (100%)

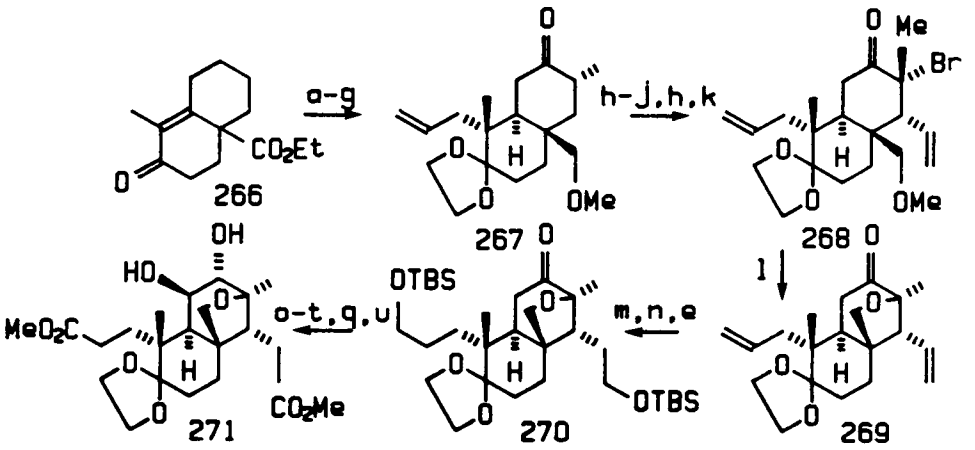
and in contrast to the difficulties experienced by Grieco[29f] in the reduction of similar systems, the lithium in ammonia reduction of 259 secured the ketone 260 with the correct C-9α(H) stereochemistry. Three different protecting groups were examined for the C-20 hydroxyl group: acetate, tert-butyldimethylsilyl (TBS) ether, and a tetrahydropyranyl (THP) ether. The first two selections were ultimately abandoned when it was found that the C-20 acetate was not compatible with a carbomethoxylation using Stiles' reagent[64] and that the removal of the C-20 TBS group was not possible in the presence of α-carbomethoxyenone functionality introduced later in the synthesis. Resolution of these problems led to the selection of the C-20 THP protecting group that is displayed in Scheme 44. Introduction of the C-13 carbomethoxy group and

chlorination-dehydrochlorination using thionyl chloride and collidine gave the α-carbomethoxyenone 261. The high-pressure Michael addition of a ketene acetal to 261 provided the adduct 262 having the correct C-14β(H) configuration and the remaining two carbons needed to assemble the D ring. Attention was next focused on the introduction of the E ring, and exposure of 263 to N-bromosuccinimide led to the α-oriented bromonium ion that intercepted the C-20 hydroxymethyl group in 263 to afford the bromodioxane 264. Initial attempts to contract the dioxane ring in 264 using a silver ion-assisted process failed, but fortunately, heating 264 in N,N-dimethyl formamide effected the desired ring contraction to the tetrahydrofuran 265 and provided an ABCE quassinoid intermediate. Continued efforts directed toward the pentacyclic intermediates will presumably take advantage of the methodology described in Scheme 28.

(e) C-BC-BCE...ABCDE Approach

As shown in Scheme 45, Grieco's efforts[29g,h] directed

Scheme 45

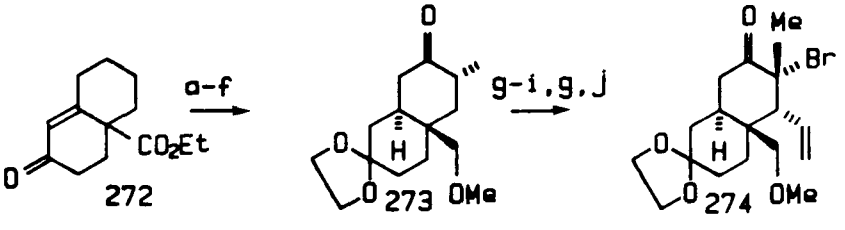


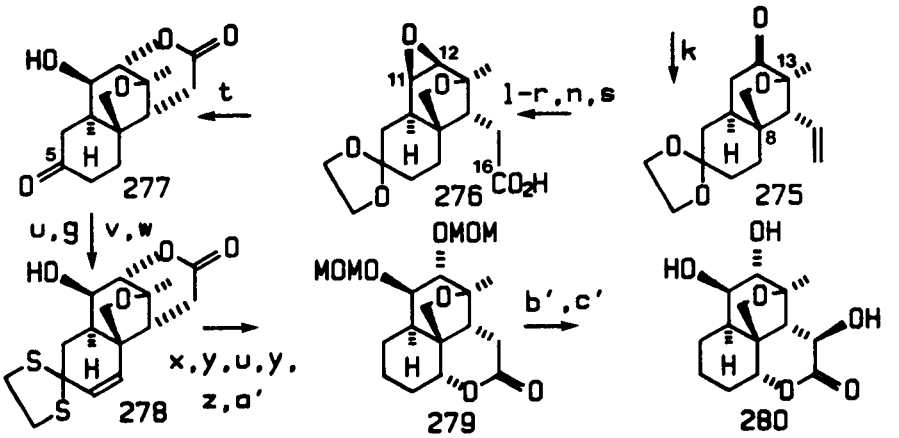
a) NaH, DMSO, CH_2=$CHCH_2Br$ b) EG, p-TsOH c) $LiAlH_4$ d) NaH, MeI e) CrO_3·2Py f) LDA, MeI g) Li, NH_3 h) TMSI i) PhSeCl followed by H_2O_2 j) CH_2=CHLi, CuI, $P(nBu)_3$ k) NBS, -23°C l) DMF, 140°C (90%) m) B_2H_6 followed by H_2O_2, HO^- n) $tBuMe_2SiCl$ o) p-$TsNHNH_2$ followed by MeLi p) n-Bu_4NF q) $(COCl)_2$, DMSO r) Ag_2O s) CH_2N_2 t) OsO_4 u) $NaBH_4$

toward the pentacyclic quassinoids involved the elaboration of the enone 266 in Scheme 45 to a BCE intermediate 271 for the synthesis of quassimarin (8). Among the crucial features of the approach in Scheme 45 were the development of a new method for the assembly of the oxymethylene bridge involving the thermal rearrangement of the α-bromoketone 268 in N,N-dimethyl formamide at 140°C that led to the tricyclic ether 269. The mechanism[29h] for this transformation presumably involved the formation of an oxallyl cation that trapped the C-20 methoxy group at C-13. Subsequent attack by bromide on the methyl group of the methoxide completed the oxymethylene bridge. The regioselectivity of the trapping process at C-13 derived from the 1,3-diaxial interactions that disfavored attack at the alternate C-11 site.

Further development[29i] of the themes in these studies ultimately led to the synthesis of an analog of quassimarin (8) lacking the A ring and the C-19 angular methyl group. As shown in Scheme 46, application of this α-bromoketone strategy

Scheme 46





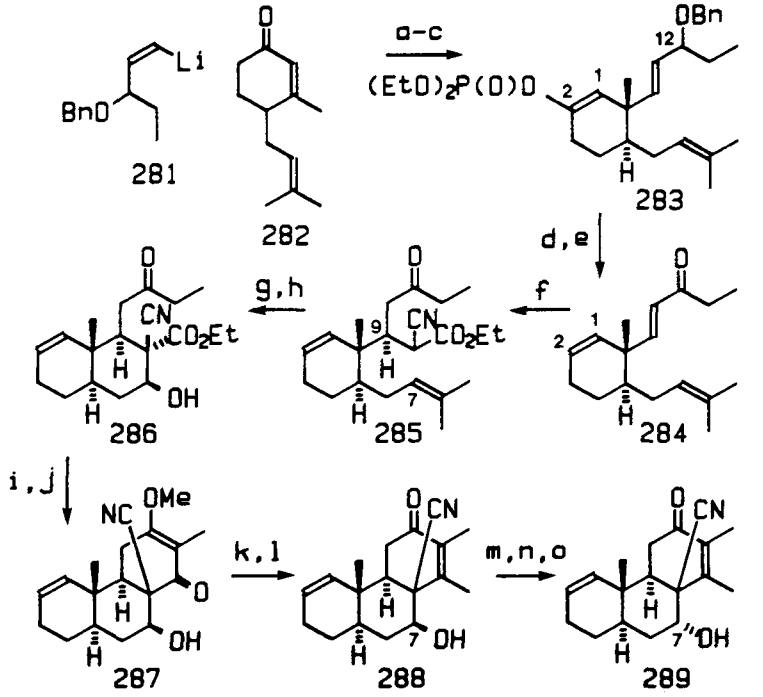
a) EG, p-TsOH b) $LiAlH_4$ c) NaH, MeI d) $CrO_3 \cdot 2Py$ e) LDA, MeI f) Li, NH_3 g) TMSI h) PhSeCl followed by H_2O_2 i) $CH_2=CHLi$, CuI, $P(nBu)_3$ j) NBS k) DMF, 150°C (75%) l) B_2H_6 followed by NaOH, H_2O_2 m) $tBuMe_2SiCl$ n) $CrO_3 \cdot 2Py$ o) $TsNHNH_2$ p) LDA q) MCPBA r) $n\text{-}Bu_4NF$ s) Ag_2O t) p-TsOH, acetone u) MOMCl v) $Pd(OAc)_2$, CH_3CN w) $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$ x) Ra(Ni) y) NaOH followed by HCl z) I_2, CH_3CN a') nBu_3SnH b') LDA, MoOPh c') BF_3, Me_2S

led to the tricyclic ketone 275 with the desired C-8,13 oxymethylene bridge. Unlike the previous route in Scheme 45, the introduction of the 11β,12α-diol functionality did not rely on the Fuchs' strategy[57] but instead involved the ring opening of a β-epoxide in 276 by the C-16 carboxylate group in order to furnish the bridged lactone 277. Conversion of the C-5 ketone in 277 to an unsaturated dithioketal in 278 set the stage for an iodolactonization that introduced the D ring in lactone 279. The oxidation of 279 following the procedure of Polonsky[9] and deprotection completed the quassimarin analog 280.

(f) A-AB-ABC-ABCD-ABCDE Approach

The imaginative route taken by Ganem[65a] provided an advanced intermediate suitable for the total synthesis of the pentacyclic quassinoids and represented a major departure from the traditional Diels-Alder and Robinson annelation strategies for assembling the perhydrophenanthrene skeleton of the quassinoids. As shown in Scheme 47, the approach began by

Scheme 47



a) CuI, Bu_3P b) n-BuLi c) $(EtO)_2POCl$, Et_3N d) Li, NH_3, t-BuOH e) $CrO_3 \cdot 2Py$ f) $CNCH_2CO_2Et$ g) O_3 h) Me_2S, $NaHCO_3$ i) LiOEt, EtOH j) $HC(OMe)_3$, p-TsOH k) MeLi l) H_3O^+ m) Jones' oxidation n) $i\text{-}Bu_2AlH$ o) MnO_2

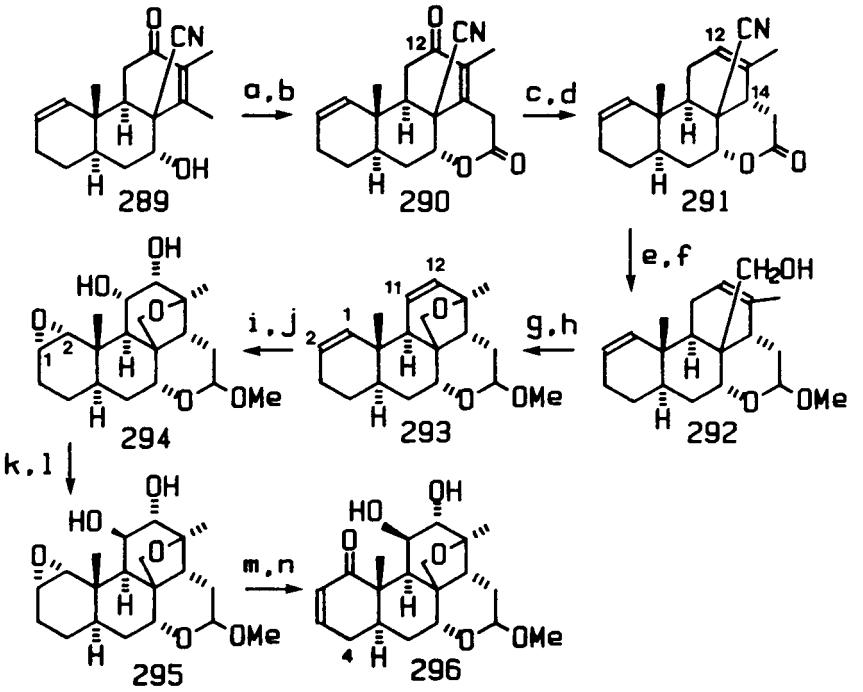
assembling the major portion of the carbon skeleton through the conjugate addition of a substituted vinyllithium 281 to enone 282 followed by trapping of the resulting enolate as its phosphate ester in 283. A Birch reduction simultaneously deprotected the C-12 benzyl ether and reductively cleaved the

phosphate ester to provide the C-1 olefin functionality, a stable, isolated functional group that would ultimately provide a "handle" for manipulating the A ring after the introduction of the B, C, D, and E rings. Deprotection of the benzyl ether at C-12 and oxidation afforded the enone 284. The stereoselective conjugate addition of ethyl cyanoacetate to the β-face of enone 284 furnished the adduct 285 with the correct stereochemistry at C-9. This stereoselectivity presumably reflected a kinetic preference for the addition of the cyanomalonate nucleophile to the β-face of the enone in a conformer such as that displayed in 284 from the side opposite the isopentenyl group.

With these skeletal fragments in place, Ganem[65a] next capitalized on the cyanoacetate residue in 285 to close the B ring. A regioselective ozonolysis of the trisubstituted C-7 alkene with concomitant condensation of the cyanoacetate and the intermediate aldehyde afforded the bicyclic alcohol 286. Construction of the C ring employed an enolate addition to the carboethoxy group and treatment with trimethyl orthoformate to afford the enone 287. The addition of methyllithium to the C-14 ketone gave the tricyclic enone 288 with the correct relative stereochemistry at all but the C-7 center. Epimerization of the C-7β alcohol required a stepwise oxidation and stereospecific reduction to obtain the C-7α alcohol 289.

Attention then turned to the construction of the D and E rings, and the treatment of enone 289 with 1,1'-carbonyldiimidazole followed by base afforded the δ-lactone 290 as shown in Scheme 48. Since the concave nature of the BCD rings in

Scheme 48



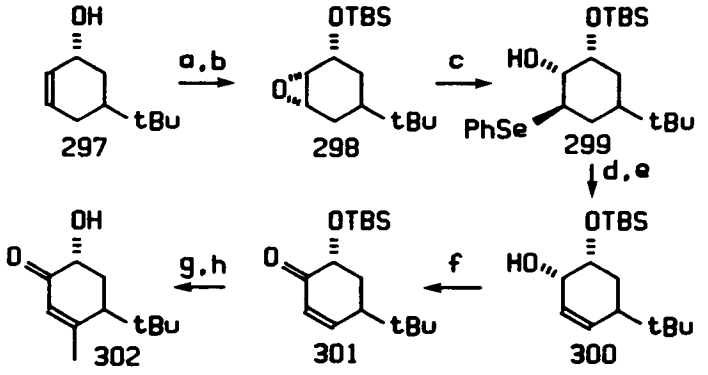
a) 1,1'-carbonyldiimidazole b) KH c) H_2NNHTs d) $NaBH_3CN$, HOAc e) i-Bu_2AlH f) H^+, MeOH g) PhSeCl h) H_2O_2 i) epoxidation j) OsO_4 k) PDC l) Bu_4NBH_4 m) PhSeNa, H_2O_2 n) $CrO_3 \cdot 2Py$

290 would direct the addition of hydride reagents to the β-face, the reductive elimination of the C-12 unsaturated tosylhydrazone derived from 290 furnished the δ-lactone 291 with the correct C-14β(H) stereochemisty. The protection of the δ-lactone 291 as the methyl acetal and the reduction of the nitrile provided the alcohol 292. Construction of the E ring employed Nicolaou's selenocyclization[54] to afford the pentacyclic olefin 293. Following the regio- and stereoselective epoxidation of the C-1 olefin, the osmium tetraoxide oxidation of the C-11 olefin gave the cis-diol 294. Conversion of 294 to the trans-diol 295 followed the Fuchs' proced-

ure,[57] and manipulation of the C-1α,2α epoxide afforded the enone 296 requiring only the addition of a C-4 methyl group and C-2 oxidation to complete a synthesis of quassimarin (8).

Efforts along these lines were reported in a model study[65b] directed toward the A ring α'-hydroxyenone functionality characteristic of several quassinoids. Significant among the findings of this particular study were the observations that the protected epoxy alcohol 298 in Scheme 49 could

Scheme 49



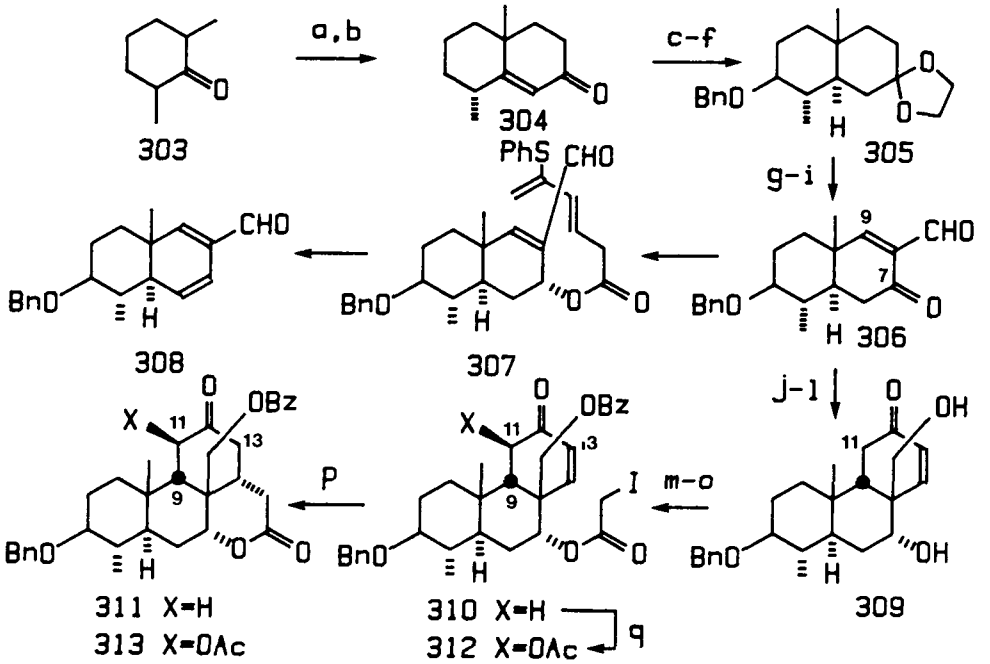
a) $VO(acac)_2$, tBuOOH b) TBSCl, imidazole c) $iBu_2AlSePh$, CH_2Cl_2, 0° d) MCPBA e) Et_3N, $ClCH_2CH_2Cl$, 65°C f) DDQ g) Me_2CuLi followed by TMSCl followed by $Pd(OAc)_2$ h) n-Bu_4NF

not be converted directly to the enediol 300. However, the use of diisobutylaluminum phenylselenide afforded the 1,2-diol 299, that was in contrast to the usual trans-diaxial preference exhibited by sodium phenylselenide. The elimination of phenylselenoxide provided the desired enediol 300. Although the enediol 300 was susceptible to over-oxidation using manganese dioxide, the DDQ oxidation of 300 furnished the enone 301, that subsequently provided the enone 302.

Our own efforts[66a] to develop an approach to the penta-

cyclic quassinoids commenced with an approach using an intramolecular Diels-Alder reaction to introduce the CD rings in a single operation. As shown in Scheme 50, beginning with the

Scheme 50



a MVK, H_2SO_4 b) NaOEt c) EG, p-TsOH d) CrO_3.2Py e) Li, NH_3 f) NaH, BnBr g) H_3O+ h) NaOMe, HCO_2Et i) DDQ or PhSeCl followed by H_2O_2 j) CH_2=C(OTMS)C(R)=CHOMe k) Red-Al l) aq. HCl, THF m) PhCOCl, Py, DMAP n) $(ClCH_2CO)_2O$, Py, DMAP o) NaI, acetone p) TMSI, Et_3N, CH_3CN q) $Mn_3O(OAc)_7$

readily available enone 304, a straightforward sequence furnished the bicyclic dienophile 306 having the desired oxygenation pattern in the A and B rings. Acetalization, stereoselective reduction of the C-7 ketone, coupling with a suitable deconjugated sorbate, and hydrolysis provided the linked diene-dienophile 307, but unfortunately, the thermal and acid-catalyzed Diels-Alder reactions of 307 led principally to the

diene aldehyde 308 and not to the desired tetracyclic adduct.

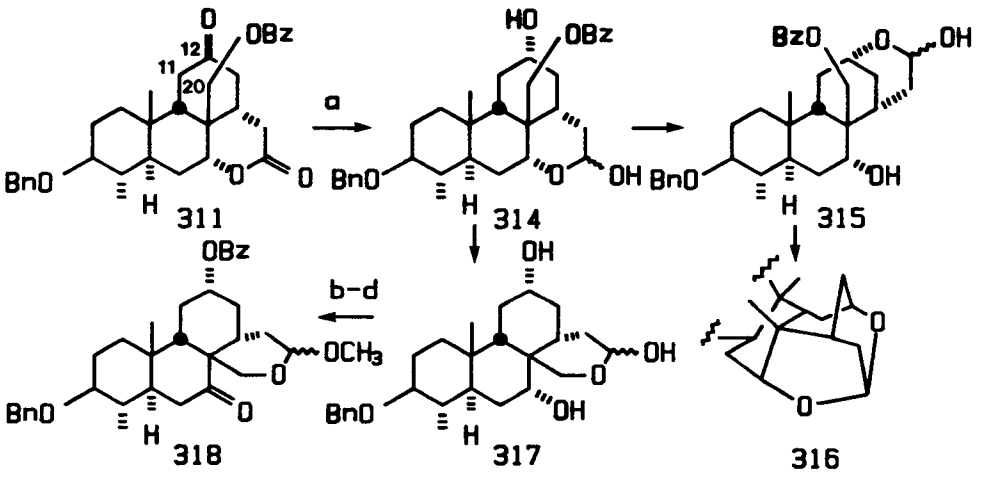
A solution to the problem of introducing the C and D rings involved the Diels-Alder reaction of the dienophile 306 in Scheme 48 with Danishefsky's diene[67] and the immediate reduction of the adduct to secure the tricyclic enone 309. After frustrating attempts to apply an intramolecular Reformatsky reaction in order to close the δ-lactone, we achieved an interesting and efficient closure of the D ring by treating the α-iodoacetate 310 with iodotrimethylsilane to give the tetracyclic δ-lactone[66b,c] 311. Cognizant that we needed to invert the C-9β stereochemistry in 311, we employed a manganese(III) acetate oxidation[68] to afford the α'-acetoxyenone 312 that also cyclized in the presence of iodotrimethylsilane to provide the tetracylic δ-lactone 313, an intermediate that we anticipated would permit the introduction of a C-11 keto group and the inversion of C-9β stereochemistry.

The first glimmer of the difficulties that we were about to encounter occurred when we attempted to prepare δ-lactones analogous to 311 or 313 but having a C-13 methyl group. We were surprised to find that the introduction of a C-13 methyl group in an enone analogous to 310 thwarted the iodotrimethylsilane-mediated cyclization[66b,c] of the α-iodoacetate to the δ-lactone. Since it appeared that this deficiency could be overcome later in the synthesis through the alkylation of a C-12(13) enolate of the C-12 ketone, we turned our attention to another, seemingly innocuous problem in the C ring: introduction of the natural C-9α(H) stereochemistry. In the course of studies designed to clear this troublesome hurdle, many

different approaches were explored, and these difficulties were, in part, a consequence of the unusual ring fusions in the tetracyclic intermediates such as 311 and 313 in Scheme 50. In this particular fused ring system, either the B, C, or D ring must occupy a boat conformation, and a number of rearrangements of this particular ring system served, as we were to discover, to relieve the strain associated with this system. In addition, the cis-fusion of the CD rings in these intermediates guaranteed the close proximity of functionality at the C-7, C-12, and C-16 centers, a fact that was also reflected in the transannular reactions that we encountered.

In the first approach to this problem, we sought to elevate the C-11 oxidation level in 311 to that of a ketone, and prior to undertaking this objective, we needed to convert the base-sensitive δ-lactone in 311 to a protected δ-lactol. A report[8] that the selective sodium borohydride or diisobutylaluminum hydride reduction of the δ-lactone in quassin (5) was possible in the presence of the C-1 and C-11 ketone groups suggested that we might also discriminate between the reduction of the δ-lactone and ketone functionality in 311 or, at the very least, that we would be able to protect the ketone functionality in 311 and then reduce the δ-lactone. In studying the reduction of 311, we observed that the rate of reduction of the three carbonyl groups in 311 decreased in the following order: C-12 ketone = lactone >> C-20 benzoate and that the cis-fusion of the BC rings in 314 dictated that the reduction of the C-12 ketone resulted an immediate transacetalization. As illustrated in Scheme 51, reduction of both

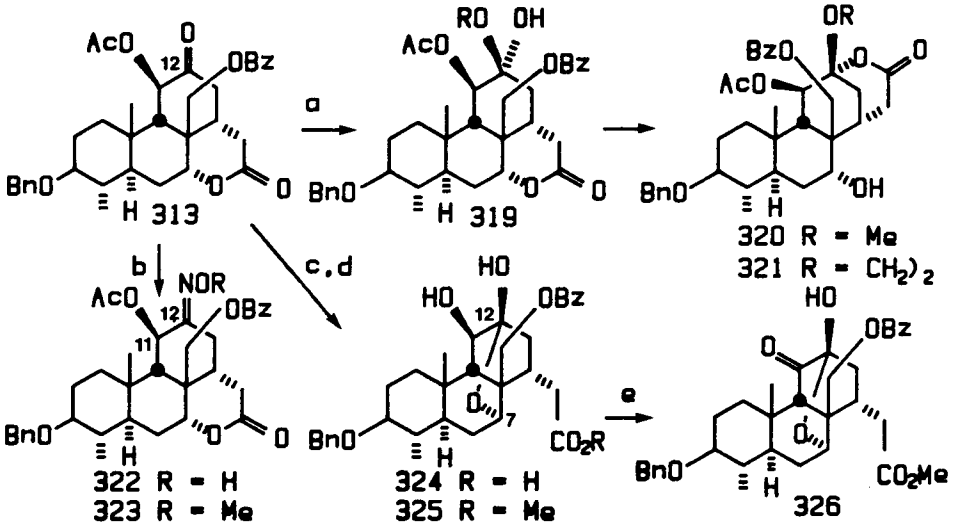
Scheme 51

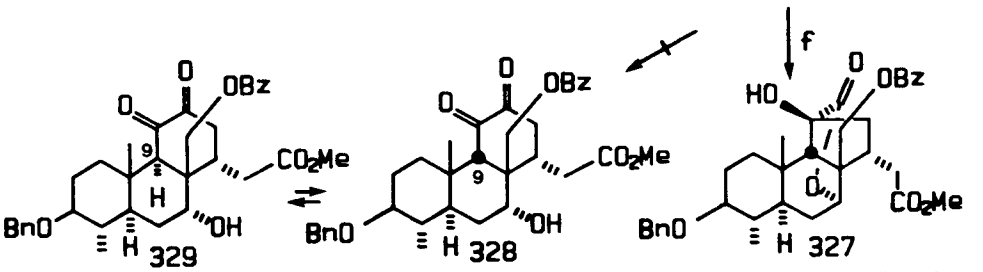


the lactone and the C-12 ketone in 311, under various conditions, furnished the rearranged lactol 315, identified as the curious acetal 316. Complete reduction of 311 led to the rearranged δ-lactol 317 that was identified as the acetal 318. Efforts to intercept 314 or identify reagents that would selectively reduce the δ-lactone in 311 were unsuccessful.

In a second approach shown in Scheme 52, we examined the

Scheme 52





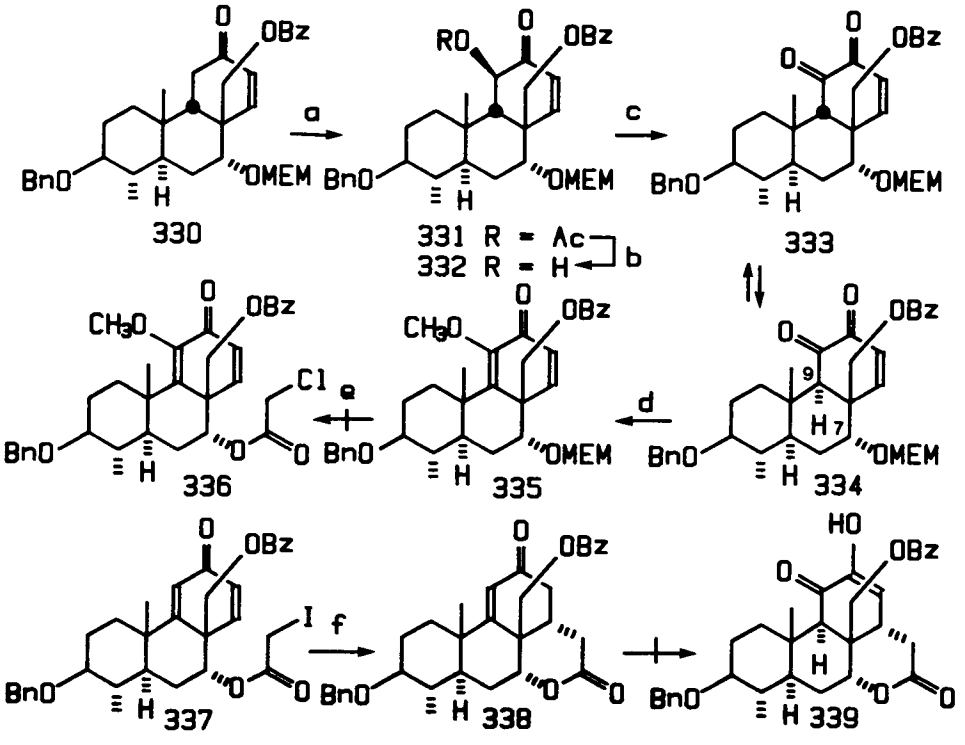
a) HCl, MeOH or EG, p-TsOH b) H_2NOH or H_2NOCH_3 c) LiOH
d) CH_2N_2 e) Swern oxidation f) various bases

selective protection of the C-12 ketone in 313. However, the intermediate hemiketal 319 derived from the reaction of 313 with either methanol or ethylene glycol underwent rapid translactonization to afford the rearranged lactones 320 and 321, respectively. Successful conversion of 313 to the oxime 322 or O-methyloxime 323, with the expectation that this change might permit differentiation between the C-12 imino center and the lactone, ultimately proved of little value when we were unable to reduce selectively the δ-lactone or manipulate the C-11 acetate in these oxime derivatives. In a third approach, that is also shown in Scheme 52, we elected temporarily to sacrifice the δ-lactone in order to correct the C-9β(H) stereochemistry. Saponification of δ-lactone 313 unveiled the C-7 hydroxyl group in the presence of the C-12 ketone and resulted in an transannular interaction leading to the hemiketal 324. Pleased at having "internally" protected the C-12 ketone, we employed a Swern oxidation[20] to secure the desired diketone 326 and set the stage for what we had hoped would be the resolution of the C-9 stereochemical problem. Efforts, however, to open the hemiketal to 328 and epimerize the recalcitrant C-9β(H) stereocenter to give the diketone 329

were thwarted by a benzilic acid rearrangement[69] that led to the lactone 327.

In a fourth assault on this problem, we attempted to invert the C-9 stereocenter prior to introducing the D ring lactone. This approach took several different directions: incorporate a substituent at C-9 (e.g., Cl, SPh) in the dienophile 306 in Scheme 50 or incorporate a substituent (e.g., OMe, SePh, SPh) in the diene that would ultimately appear at C-11 in enone 309 in Scheme 50. Unfortunately, these efforts also failed, and as an alternative, we converted the enone 330 in Scheme 53 to cyclohexenedione 334 to which we tentatively

Scheme 53



a) $Mn_3O(OAc)_7$ b) LiOH, aq. THF c) Swern oxidation d) $[Me_3O]BF_4$ e) $FeCl_3$, $(ClCH_2CO)_2O$ f) TMSI, Et_3N, CH_3CN

assigned the desired C-9 stereochemistry. Success, in terms

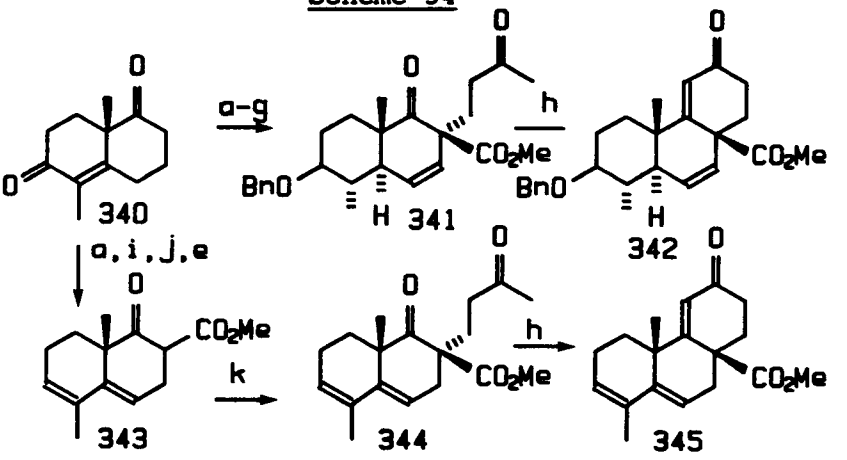
of a quassinoid synthesis, hinged upon the selection of an appropriate C-7 hydroxyl protecting group that could be removed at either cyclohexenedione 334 or cyclohexadienone 335 stage in order to introduce the progenitor of the δ-lactone. Consequently, we developed a selective procedure for the direct conversion of a 2-(methoxyethoxy)methyl (MEM) protecting group to an acetate or α-chloroacetate ester,[70] but despite success in model systems, application of this selective deprotection procedure and others to the critical substrates such as 335 failed to give the α-chloroacetate 336. In a final approach, we prepared the cyclohexadienone 337 in Scheme 53, and successfully converted this to the desired enone 338 in which the C-9β(H) stereochemistry was obliterated. In the course of studies leading up to this objective, we concurrently developed a satisfactory procedure for the conversion of model enones to diosphenols that involved the hydroxylation of enones with osmium tetroxide and barium chlorate[71] followed by an acid-catalyzed dehydration of the intermediate α,β-dihydroxyketone to deliver a diosphenol in excellent overall yield. Although we recognized that the enone in 338 was hindered, other investigators had successfully manipulated similarly hindered enones in quassinoid systems.[47,72] However, the application of this methodology to the enone 338 failed to produce the diosphenol 339, and this approach was finally abandoned in favor of an enantioselective route to be described later.

(g) B-AB-ABC-ABCE-ABCDE Approach

We and others investigated an approach in which the

Robinson annelation of a bicyclic β-ketoester with methyl vinyl ketone would afford a bicyclic 1,5-diketone[73] 341 shown in Scheme 54, but we were unable to complete the crucial aldol

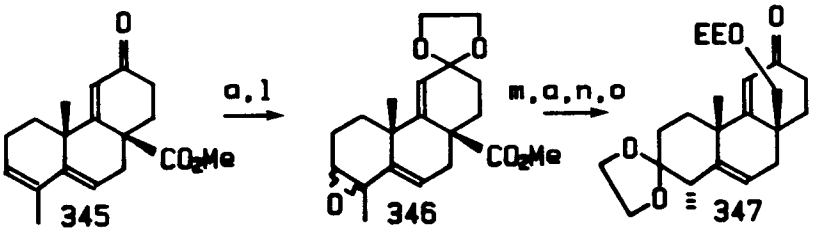
Scheme 54

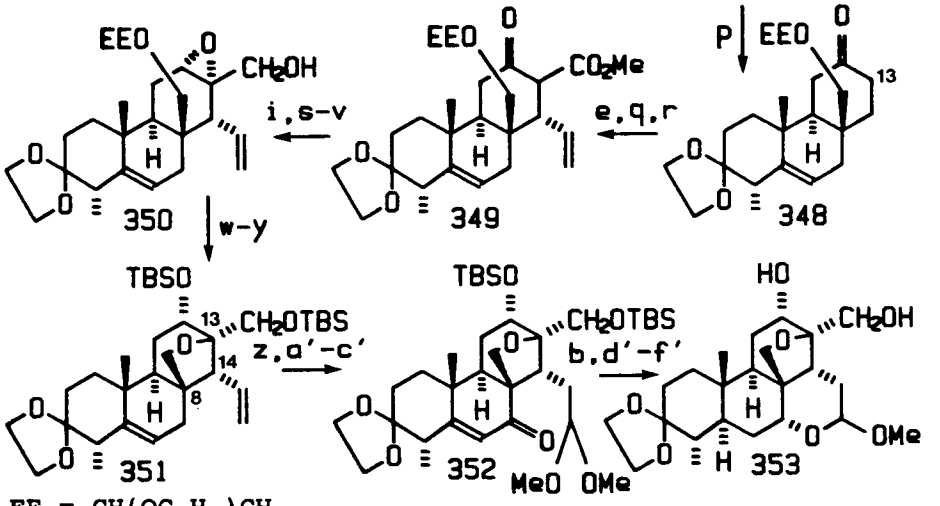


a) EG, p-TsOH b) Li, NH_3, t-BuOH c) NaH, BnBr d) 1:2:3 1M HCl:HOAc:THF e) NaH, KH (cat.), $(MeO)_2CO$ f) NaH, PhSeCl followed by H_2O_2 g) Triton B, MVK h) pyrrolidine, m-$CH_3C_6H_4SO_3H$ or piperidine, $PhCO_2H$, benzene, 80°C i) $NaBH_4$ j) HCl, HOAc, MeOH, heat k) NaOMe, MVK

condensation-dehydration step to obtain the tricylic enone 342. Murae and Takahashi[72] investigated this same approach using a slightly different 1,5-diketone 344 and succeeded in obtaining the tricyclic enone 345 in Scheme 54 as well as a related enone having an angular methyl group in place of the angular carbomethoxy group in 345. As shown in Scheme 55, the

Scheme 55





EE = $CH(OC_2H_5)CH_3$

l) MCPBA m) $BF_3 \cdot Et_2O$, $HOCH_2CH_2OH$ n) $LiAlH_4$ o) PPTS, CH_2=CHOEt p) NaHTe, EtOH (98%) q) NaH, PhSeCl followed by H_2O_2 r) CH_2=$CHMgBr$, CuI, $P(nBu)_3$ (80%) s) MsCl, Et_3N t) DBU, C_6H_6, 80°C u) $i\text{-}Bu_2AlH$ v) t-BuOOH, $Ti(OiPr)_4$, -20° w) PPTS (cat.), EtOH (100%) x) TBSCl, imidazole y) TBSCl, KH z) thexylborane followed by H_2O_2 a') $CrO_3 \cdot 2Py$ b') $HC(OMe)_3$, p-TsOH, CH_2Cl_2 c') CrO_3, 3,5-dimethylpyrazole d') $LiBH(Et)_3$, -78° e') PPTS, MeOH f') $n\text{-}Bu_4NF$

enone 345 served admirably for the synthesis of a pentacyclic quassinoid intermediate 353. In this approach, several straightforward transformations of the enone 245 furnished enone 347 that was reduced using sodium hydrotelluride to give the trans-fused BC ketone 348. Regioselective carbomethoxylation at C-13 in 348, dehydrogenation using the Reich-Sharpless procedure,[74] and conjugate addition of a vinyl cuprate reagent introduced the two remaining carbons, C-15 and C-16, of the quassinoid skeleton. Further manipulations of the β-ketoester functionality in the C ring of 349 took advantage of the Sharpless allylic oxidation procedure[75] to acquire regioselec-

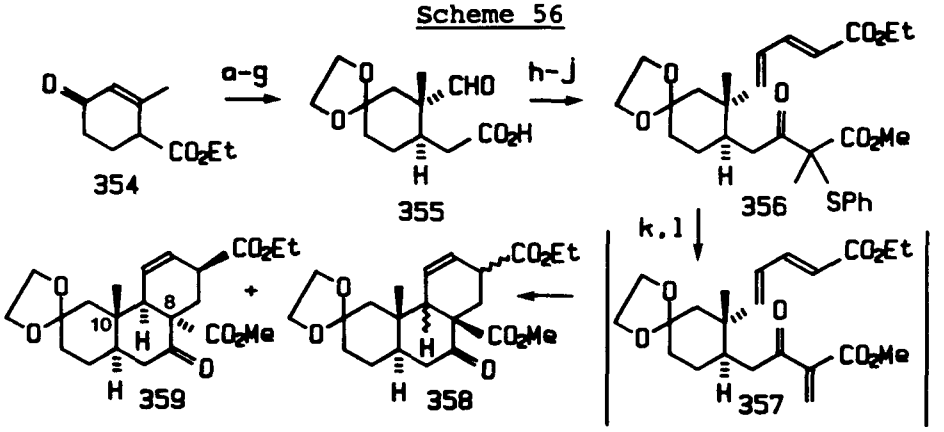
tively the epoxy alcohol 350. A subsequent publication[72b] outlined a slightly different sequence interconnecting the enone 345 and the ketal 350 that was more amenable to large scale work.

Acid-catalyzed deprotection of the C-20 ethoxyethyl group and subsequent ring opening of the epoxide furnished the tetracyclic ether 351 in yet another solution to the problem of introducing the C-8,13 oxymethylene bridge. Further hydroboration-oxidation of the C-14α vinyl group and the allylic oxidation of the B ring furnished the enone 352 and a stereoselective reduction provided the pentacyclic intermediate 353. Completion of a quassinoid synthesis from this intermediate requires only the elevation of the oxidation state in the A and C rings, and recent publication[8c] indicated that a racemic synthesis of 23 in Scheme 4 was completed that, in conjunction with the conversion of naturally derived 23 to bruceantin (25), served to complete a formal total synthesis of 25.

(h) A-ABC....ABCDE Approach

Hoye[76] envisioned an approach to the pentacyclic quassinoids that was conceptually related to the Kametani approach[38,39] but that was readily able to accommodate a functionalized C-8 angular substituent needed ultimately in order to construct the E ring. The conversion of Hagemann's ester (354) to the α-thiophenoxy β-ketoester derivative 356 and pyrolysis of the derived sulfoxide generated a reactive α-carbomethoxy acrylate dienophile[77] 357 that is shown in Scheme 56. The intramolecular Diels-Alder reaction of 357

Scheme 56



a) CH_2=CHMgBr, CuI b) EG, p-TsOH c) Red-Al d) p-TsCl e) NaCN f) KOH g) O_3 h) NaH, $(EtO)_2P(O)CH_2CH=CHCO_2Et$ i) $(COCl)_2$ j) $LiC(CH_3)(SPh)CO_2Me$ k) MCPBA l) 80°

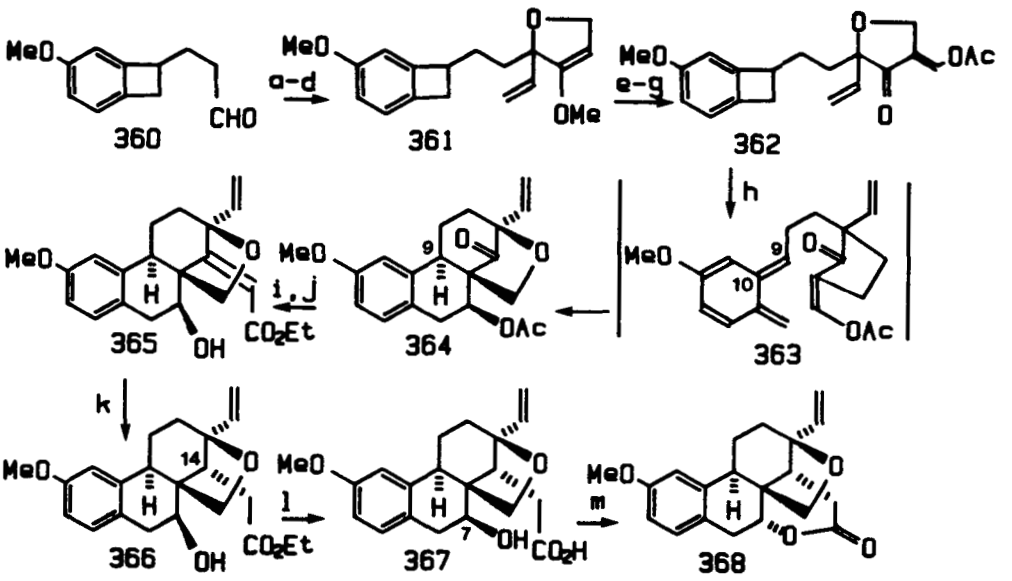
produced a 5:7 mixture of the ketoesters 358 and 359, respectively, and related examples bearing C-4 or C-14 substituents also give similar mixtures of adducts. Unfortunately, the predominant keto ester 359 derived from a transition state in which the ketone carbonyl adopted an endo-orientation with respect to the diene and consequently the adduct 359 possessed the incorrect relative configuration of the C-8 and C-10 angular substituents for a quassinoid synthesis.

(i) A-AE-ABCE-ABCDE Approach

Although Kametani's tetracyclic intermediate[38] 120 in Scheme 22 possessed many attractive features characteristic of the quassinoids, the C-8β,13β ethylene bridge in 120 was not ideally suited for the preparation of pentacyclic quassinoids having the C-8β,13β oxymethylene bridge. In a subsequent study using the same intramolecular Diels-Alder strategy, Fukumoto and Kametani[78a,b] addressed this concern in the development of a potential route to bruceantin (25). In this

instance, the aldehyde 360 in Scheme 57 was elaborated to the

Scheme 57



a) $H_2C{=}CHMgBr$ b) PCC c) nBuLi, $CH_3OCH{=}C{=}CH_2$ d) t-BuOK, 18-crown-6 e) 6M HCl f) NaH, HCO_2Et g) Ac_2O h) 180° (75%) i) NaOH, aq. MeOH j) NaH, $(EtO)_2P(O)CH_2CO_2Et$, (91%) k) Te, $NaBH_4$ (84%) l) KOH, EtOH (100%) m) MsCl, Et_3N followed by $NaHCO_3$, H_2O followed by H^+ (71%)

furanone 362 using a sequence developed by Magnus.[79] The thermolysis of 362 generated the ortho-quinodimethane that trapped the β-acetoxyenone dienophile to give the tetracyclic adduct 364 as a 6:1 mixture of C-9α and C-9β epimers, respectively. As in the preceding intramolecular Diels-Alder reaction in Scheme 22, if we assumed that the ring opening of the benzocyclobutene generated the C-9,10 E-stereochemistry shown in 363 and if we assumed that the β-acetoxyenone possessed the E-stereochemistry, the Diels-Alder reaction involving an exo-addition would generate the adduct 364 having the C-9α(H) stereochemistry.

As shown in Scheme 57, the further elaboration of 364

involved several interesting reactions commencing with the Horner-Emmons phosphonate Wittig reaction to afford an α,β-unsaturated ester 365 that was in turn stereoselectively reduced using sodium hydrotelluride to give the saturated ester 366 with the desired C-14β(H) stereochemistry. Lactonization with inversion at C-7 completed the introduction of the D ring in 368. The use of the furanone-based dienophile 362 in Scheme 57 rather than the cyclopentenone-based dienophile 118 in Scheme 22 had the distinct advantage of introducing the desired C-8β,13β oxymethylene bridge.

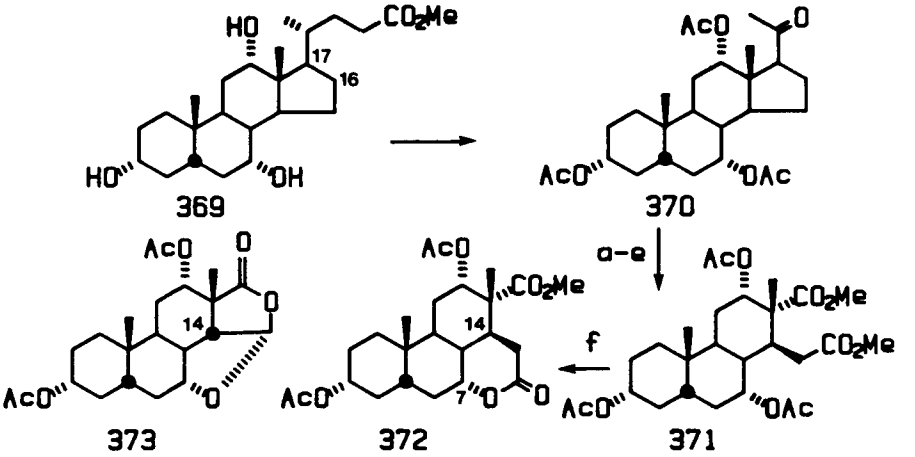
b. Enantioselective Synthetic Ventures

1. Tetracyclic Skeletons

Several groups have investigated enantioselective routes to the quassinoids using various chiral source materials. Given the similarity of the perhydrophenanthrene skeletal subunit of both the quassinoids and steroids, it was not surprising that several early investigations focused on the problems associated with the manipulation of the D ring of steroids in order to introduce the δ-lactone as well as the C-8β angular methyl group of the quassinoids. Recognition that the cleavage of the steroid D ring at the C-16,17 position would furnish a two-carbon appendage at C-14 immediately suggested the selection of the C-7α hydroxylated cholic acids as suitable starting materials since the C-7α hydroxyl group would facilitate δ-lactone construction. Dias[80] utilized just such a strategy in the degradation of cholic acid to obtain an intermediate related to the tetracyclic quassinoid skeleton. As

outlined in Scheme 58, the route began with the Barbier-

Scheme 58



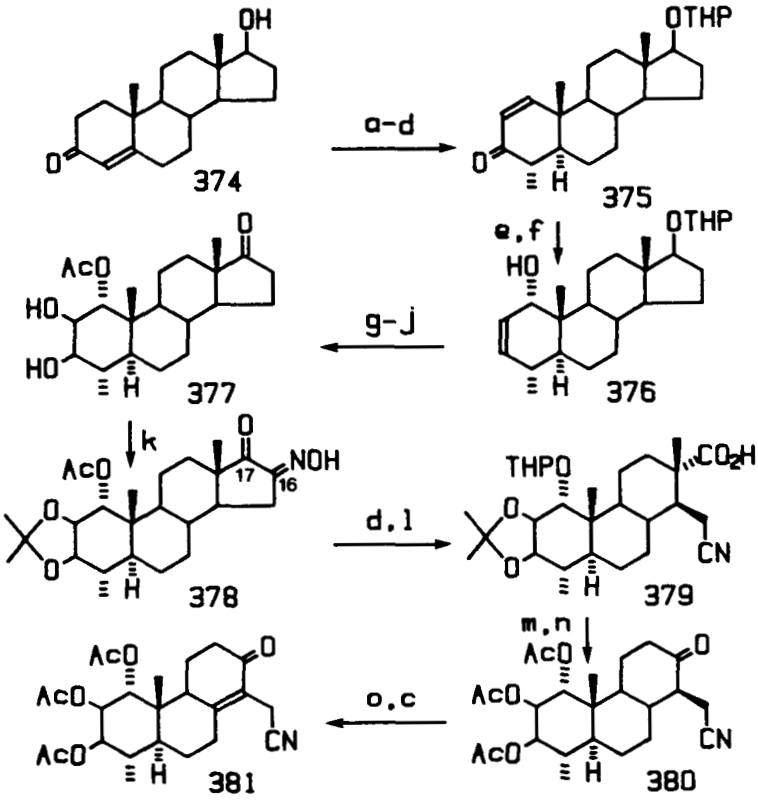
a) Br_2 b) HMPA, heat c) O_3 d) AcOH, H_2O_2 e) CH_2N_2 f) KOH, MeOH

Wieland degradation of the C-17 side-chain of methyl cholate (369) to afford the 5β-pregnan-20-one 370. To provide the necessary elements for the introduction of the δ-lactone, Dias[80] cleaved the steroid D ring at the C-16,17 bond using a bromination, dehydrobromination, and ozonolysis sequence. Lactonization of the dicarboxylic ester 371 furnished the δ-lactone 372 having the correct C-7β(H) but incorrect C-14α(H) stereochemistry. A related study[80e] involving the degradation of a 5β-androst-15-en-17-one did lead, however, to another intermediate 373, shown in Scheme 58, in which the correct C-14β(H) configuration was present. Although lactones 372 and 373 possessed a pattern of functionality and stereochemical features suitable for a quassinoid synthesis, the further progression of these intermediates would require a solution to the problem of introducing a C-8β angular methyl group as well as closing the δ-lactone.

An intriguing solution to both of these problems began in

Scheme 59 in which Graf[2] employed testosterone (374) as the

Scheme 59



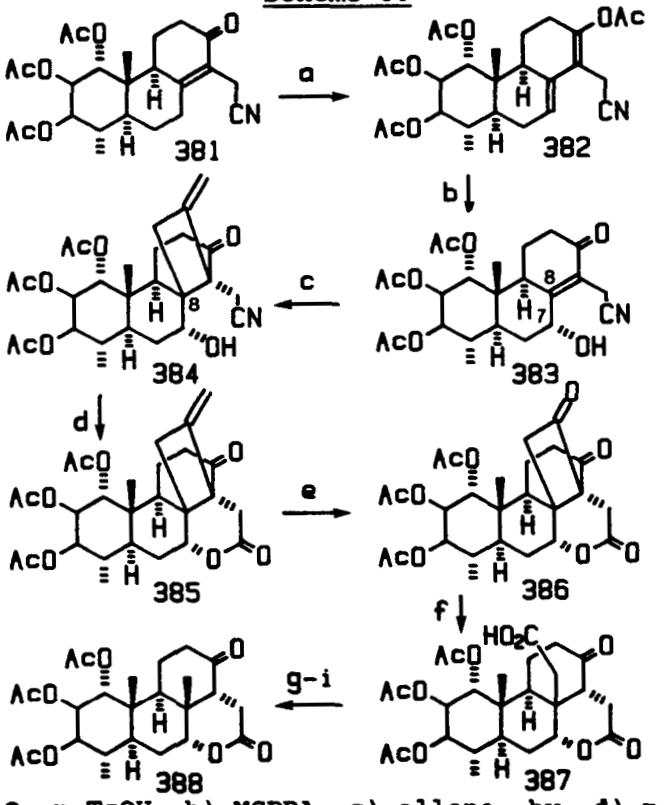
a) Li, NH_3, MeI b) Br_2 c) LiBr, Li_2CO_3 d) DHP, PPTS e) H_2O_2, KOH f) N_2H_4 g) Ac_2O h) H_3O^+ i) PCC j) OsO_4 k) $C_5H_{12}NO$, KOH l) $Pb(OAc)_4$, DMSO m) $Cu(OAc)_2$, Py n) O_3 o) $[C_6H_5NH]^+Br_3^-$

starting material. A series of A ring manipulations elevated the oxidation level at C-1 and C-2 and installed the C-4 methyl group. The reductive methylation of 374 and subsequent bromination and dehydrobromination provided enone 375. Epoxidation, Wharton rearrangement[46] of the α,β-epoxyketone, and osmylation of the allylic alcohol completed the functionalization of the A ring. This pattern of functionality was deliberately installed as a progenitor of the diosphenol function-

ality characteristic of many quassinoids. Graf[2] cleaved the steroid D ring at the C-16,17 bond using a base-catalyzed cleavage of the tetrahydropyranyl ether of the α-keto oxime 378 in order to obtain the nitrile 379. Decarboxylation and ozonolysis of the resulting exocyclic olefin at C-13 afforded the ketone 380, and the bromination and dehydrobromination furnished the enone 381, the key intermediate needed for the introduction of the C-8β angular methyl group.

As shown in Scheme 60, the peracid oxidation of the

Scheme 60



a) Ac_2O, p-TsOH b) MCPBA c) allene, hv d) p-TsOH e) O_3 f) Et_3N g) $(COCl)_2$ h) PhSeOH, Py i) n-Bu_3SnH, AIBN

dienol acetate 382 gave an intermediate 383 bearing the C-7α hydroxyl group, a structural feature that Dias[80] had incorpo-

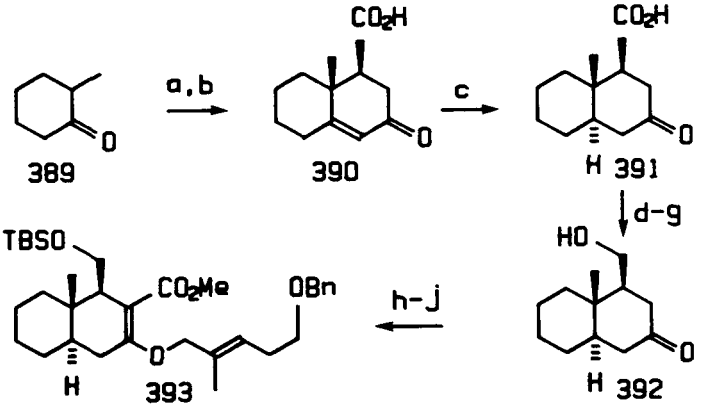
rated through judicious choice of cholic acid as a starting material. The introduction of the C-8β angular methyl commenced with the photochemical [2+2] cycloaddition of allene to enone 383 that gave the methylenecyclobutane 384. The addition of allene to the β-face was attributed to the steric influence of the axial C-7α hydroxyl group. Introduction of the δ-lactone and ozonolysis of the methylenecyclobutane 385 delivered the 1,3-diketone 386 that cleaved to furnish the keto acid 387. The reduction[81] of the phenylselenyl ester of 387 provided the C-8β angular methyl group in an intermediate having the correct configuration at all seven stereocenters along with appropriate functionality in the A and C rings necessary to complete a synthesis of a tetracyclic quassinoid.

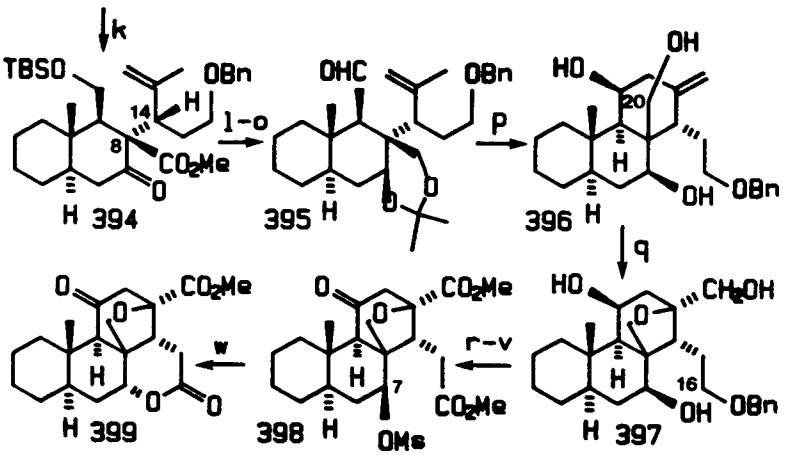
2. Pentacyclic Skeletons

(a) A-AB-ABC-ABCE-ABCDE Approach

A recent effort by Ziegler[82] highlights a particularly innovative approach that employed a terpene, (+)-carvone, as the "chiral pool" source. Although the initial route[82a] shown in Scheme 61 employed the racemic decalone 391, a subsequent

Scheme 61

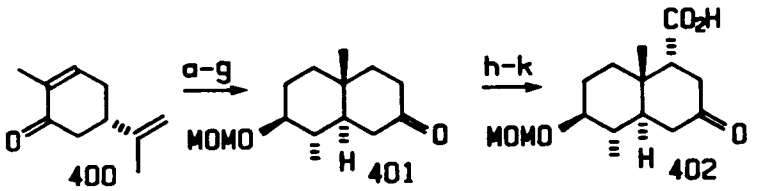




a) $CH_3COCH=CHCO_2Me$, p-TsOH b) NaOH, aq. MeOH c) Li, NH_3 d) CH_2N_2 e) $HC(OEt)_3$, MeOH, p-TsOH f) $LiAlH_4$ g) H_3O^+ h) TBSCl, imidazole i) LDA, $CH_3OC(O)CN$ j) t-BuOK, $BnOCH_2CH_2CH=C(CH_3)CH_2Br$ k) 140°C l) $LiAlH_4$ m) acetone, H^+ n) $n\text{-}Bu_4NF$ o) PCC p) $SnCl_2$ q) MCPBA r) H_2 s) [O] t) CH_2N_2 u) $LiB[CH(Me)Et]_3H$ v) MsCl, Py w) K_2CO_3, MeOH

paper[82b] described the preparation of the correct antipode of 402 for a quassinoid synthesis beginning with (+)-carvone (400) as shown in Scheme 62. Since the goal of this plan is

Scheme 62



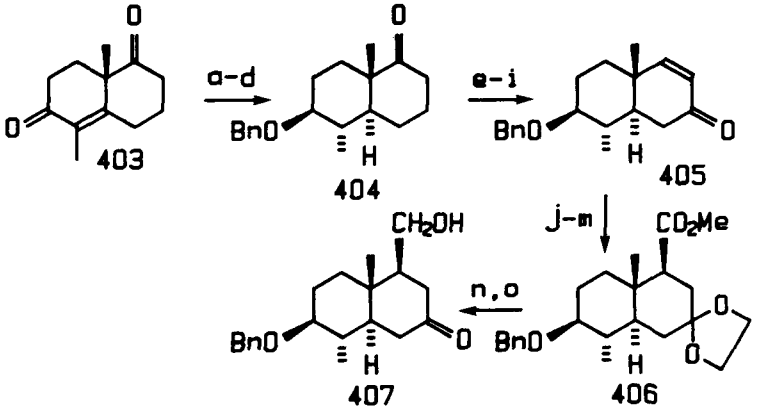
a) Li bronze, NH_3 followed by EVK and KOH, MeOH b) Li bronze, NH_3, t-BuOH c) $ClCH_2OMe$, $i\text{-}Pr_2NEt$ d) O_3 e) MCPBA f) LiOH g) PCC h) PhSeCl, H_2O_2 i) KCN, NH_4Cl, aq. DMF j) EG k) KOH, DEG, 180°C

clearly the development of an enantioselective synthesis, we have presented the discussion of both the racemic and enantioselective efforts here.

In a creative departure from the traditional course of steroid and higher terpene syntheses, Ziegler's[82a] approach

addressed the C-14β(H) stereochemical issue prior to ring CD construction using a Claisen rearrangement process. In the route that employed racemic intermediates in Scheme 61, the preparation of the putative allyl vinyl ether 393 traversed the ketoacid[83] 391 and the keto alcohol 392 as intermediates in route to 393. A substituted but racemic version of a keto alcohol 407 with A ring functionality was also available as shown in Scheme 63, but the progression of this intermediate

Scheme 63



a) p-TsOH, EG b) Li bronze c) NaH, BnBr d) H_3O^+ e) LDA, TMSCl followed by Br_2 f) DBU g) H_2O_2, NaOH h) H_2NNH_2, HOAc i) MnO_2 j) KCN, NH_4Cl, aq. DMF k) $CH(OMe)_3$, p-TsOH l) KOH, DEG, 180°C m) CH_2N_2 n) $LiAlH_4$ o) H_3O^+

to an advanced stage has not yet been described in the literature, and consequently, we will focus just on the route derived from keto alcohol 392 in Scheme 61.

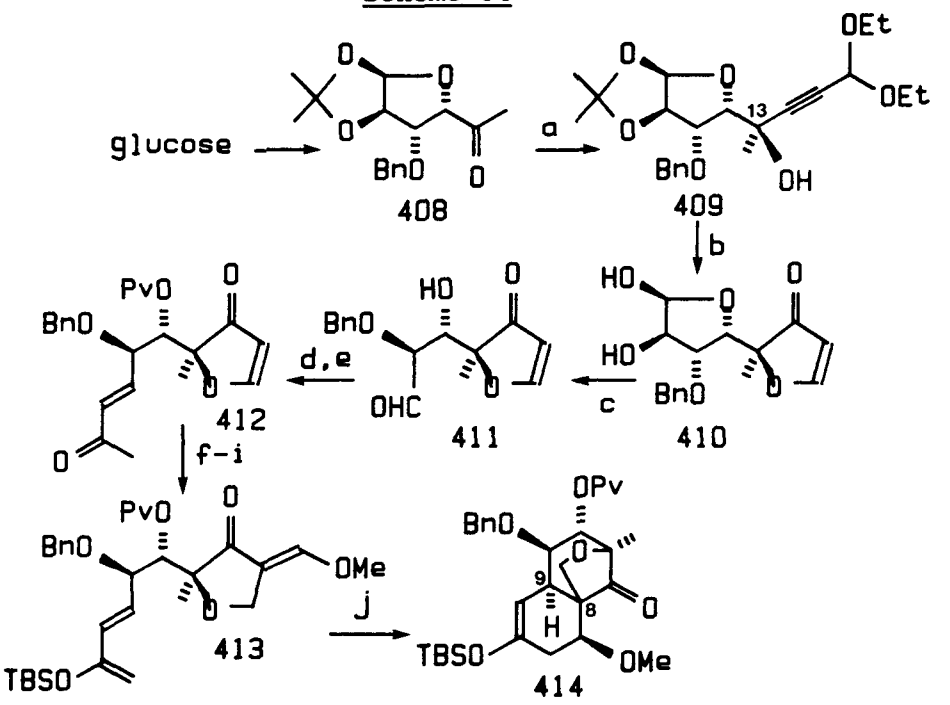
The Claisen rearrangement of 393 through a chair-like transition state secured the keto ester 394 having the correct relative configuration at the newly introduced C-8 and C-14β(H) centers. With the fragments of the C and D rings in place, a Lewis acid-catalyzed "ene" reaction, that proceeded

with concomitant deprotection of the acetonide, furnished the tricyclic triol 396. Construction of the E ring involved an epoxidation of the exocyclic olefin in 396 followed by ring opening of the 13α,21α-epoxide by the C-20 alcohol to provide the tetracyclic triol 397. Deprotection of the C-16 benzyl ether, oxidation, and a regio- and stereoselective reduction of a C-7 ketone led to a tricyclic alcohol with the incorrect C-7α(H) configuration. The base-catalyzed displacement of the C-7β mesylate by the C-16 carboxylate afforded the pentacyclic lactone 399 with the correct C-7β(H) stereochemistry. Although Ziegler suggested[82b] that the application of the sequence in Scheme 61 to the nonracemic ketoacid 402 encountered some difficulties with regard to the MOM protecting group at C-3, the utilization of other C-3 protecting groups in conjunction with this imaginative route seems likely to provide a satisfactory solution to the total synthesis of quassinoids.

(b) E-BCE....ABCDE Approach

An ingenious solution to the sterochemical problems of the C ring of quassimarin (8) involved the recognition by Schlessinger[84] of "hidden carbohydrate symmetry"[85] in that α-D-glucose possessed the correct absolute stereochemistry required at C-11 and C-12. As expected on the basis of the Felkin-Ahn rules,[86] the addition of 1-lithio-3,3-ethoxypropyne to the furanone 408 provided the propargylic alcohol 409 that has the correct stereochemistry for elaboration of the C-13 center of the quassinoids as shown in Scheme 64. Hydrol-

Scheme 64



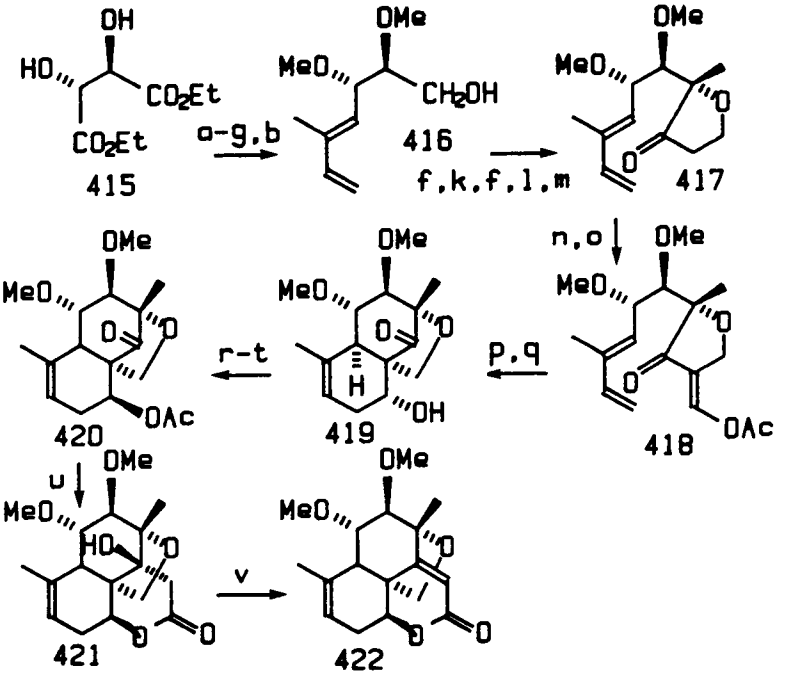
a) $LiC{\equiv}CCH(OEt)_2$, -78°C (87%) b) 6N H_2SO_4, THF, 40°C (81%) c) $NaIO_4$, $NaHCO_3$ d) $Ph_3P{=}CHCOCH_3$ e) PrCl f) TBSOTf, Et_3N g) L-selectride h) NaH, HCO_2Et i) K_2CO_3, Me_2SO_4 j) $Al(CH_3)_3$, CH_2Cl_2, -20°C (62%)

ysis of both the acetal and the acetonide centers furnished the furanone 410. Cleavage of the ribose ring and Wittig homologation of the aldehyde 411 gave, after pivaloyl ester formation, the enone 412. Conversion of the enone to the tert-butyldimethylsilyl dienol ether and elaboration of the exocyclic methoxymethylene derivative of the furanone provided an intermediate reminiscent of Kametani's intermediates (Scheme 22 and 57) and set the stage for the crucial Diels-Alder reaction in which the dienophile added to the β-face of the diene in an exocyclic mode, in agreement both with calculations and Kametani's results, to ensure the correct C-8 and

C-9 stereochemistry in the adduct 414.

In a continuation of the routes in Schemes 22 and 57, Fukumoto and Kametani[87] also reported an approach to a chiral, tetracyclic BCDE intermediate 422 in Scheme 65 that paralleled

Scheme 65



a) NaH, MeI b) $LiAlH_4$ c) BnBr, NaH, DMF d) TBSCl e) Li, NH_3, EtOH f) Swern oxidation g) $Ph_3P{=}C(CH_3)CO_2Me$ h) MnO_2 i) $Ph_3P{=}CH_2$ j) n-Bu_4NF k) MeMgBr l) n-BuLi, $MeOCH{=}C{=}CH_2$, $MgBr_2$ m) t-BuOK, 18-crown-6 followed by HCl n) NaH, HCO_2Et o) Ac_2O, Py, DMAP p) 150°C q) LiOH r) Swern oxidation s) $LiBHEt_3$ t) Ac_2O, Py, DMAP u) LDA (92%) v) $SOCl_2$, Py

the Schlessinger approach[84] in Scheme 64. In this instance, L-(+)-diethyl tartrate rather than α-D-glucose served as the "chiral pool" starting material for the preparation of furanone 418 and unlike the Schlessinger route,[84] provided a quassinoid intermediate with the unnatural absolute configuration.

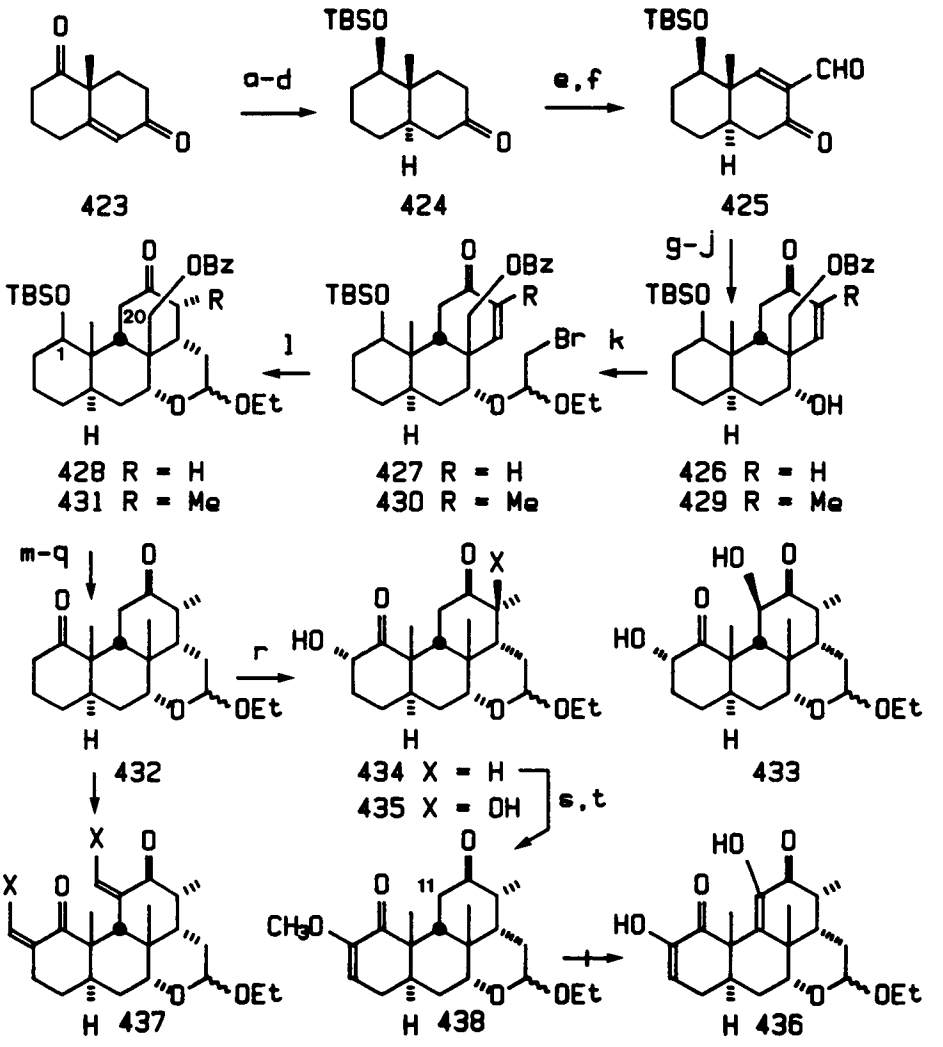
The Diels-Alder reaction of 418 provided both the adduct 419 and its C-9β(H) epimer in a 30 to 1 ratio in 83% yield,[87b] and unlike the previous results, an endocyclic mode of addition of the furanone dienophile to the β-face of the diene accounted for the stereochemistry of the principal adduct 419. Subsequent transformations[87b] of the adduct 419 included the inversion at C-7 to afford the acetate 420 and a Claisen condensation to introduce the D ring. Efforts to remove the superfluous C-14β hydroxyl group in 421 via the α,β-unsaturated lactone 422 were, however, unsuccessful.

(c) A-AB-ABC-ABCD...ABCDE Approach

Several considerations guided the redesign of our original synthetic route[66] to racemic quassinoids (Scheme 50) in order to achieve an efficient entry to enantiomerically pure intermediates with functionality suitable for the quassinoids. First, we sought to avoid the problems that involved the selective manipulation of both a C-12 ketone and a δ-lactone in the same intermediate, and consequently, we required a procedure for the direct introduction of a protected δ-lactol in the presence of a C-12 ketone. Secondly, we wanted to develop an advanced intermediate sufficiently versatile to reach both the tetracyclic and pentacyclic quassinoids. The redesigned route[88] originated from the (-)-enantiomer of the Wieland-Miescher ketone (423) prepared using R-proline,[89] and the crucial, successful step in this plan was the free radical cyclization[90] of the bromoacetals[91] 427 and 430 to deliver the protected lactols 428 and 431, respectively, as shown in

Scheme 66. It was gratifying that this cyclization, unlike

Scheme 66



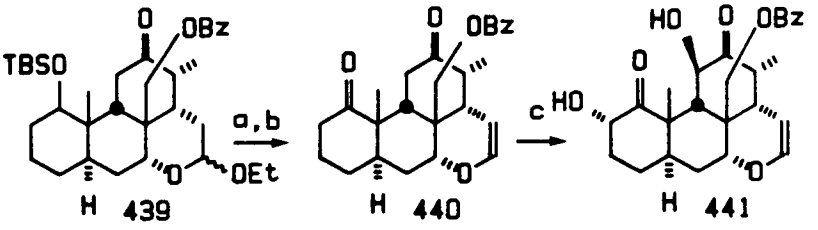
a) $NaBH_4$ b) TBSCl c) Li, NH_3, t-BuOH d) PCC e) NaH, HCO_2Et f) PhSeCl followed by H_2O_2 g) CH_2=C(OTMS)CH=CH-OMe or CH_2=C(OTMS)C(CH_3)=CHOMe h) Red-Al i) H_3O+ j) PhCOCl, Py, DMAP k) $BrCH_2CH(OMe)Br$, $PhNMe_2$ l) n-Bu_3SnH m) K_2CO_3, MeOH n) PhOC(=S)Cl o) n-Bu_3SnH p) n-Bu_4NF q) PCC r) LDA or $LiN(TMS)_2$ followed by MoOPh s) Swern oxidation t) NaOMe, DMSO, MeI

the iodotrimethylsilane-mediated cyclization[66b,d] described earlier, was compatible with a C-13 methyl group, a finding

that we saw as a favorable augury.

We next diverted the δ-lactol 431, that was developed specifically for the pentacyclic quassinoids, toward the synthesis of a tetracyclic quassinoid. This direction required, among other transformations, the removal of the C-20 benzoate group in 431, deprotection of the C-1 TBS ether, and oxidation to obtain the diketone 432 in Scheme 66. Despite reports[29] of a successful MoOPH oxidation of a bis(enolate) of a similar diketone, all efforts to oxidize the bis(enolate) of 432 to the desired bis(α-ketol) 433 failed: we isolated only the α-ketol 434 and the bis(α-ketol) 435 using a variety of oxidants (e.g., MoOPH, Davis' reagent, etc.). Other procedures such as the direct oxidation of the bis(enolate) of the diketone 432 to the bis(diosphenol) 436, the lead tetraacetate or m-chloroperxoybenzoic acid oxidation of a bis(trimethylsilyl) enol ether,[45b] or the preparation of a C-2,11 bis(hydroxymethylene), bis(eneamine), or bis(enone) adducts related to 437 were also unsuccessful. Efforts to block the C-13 position (e.g., bis(phenylsulfenylation) at C-2 and C-13) prior to an enolate oxidation at C-11 or efforts to oxidize the C-2 blocked derivative 438 at C-11 were also unrewarding. In a similar vein, as shown in Scheme 67, deprotection of the

Scheme 67

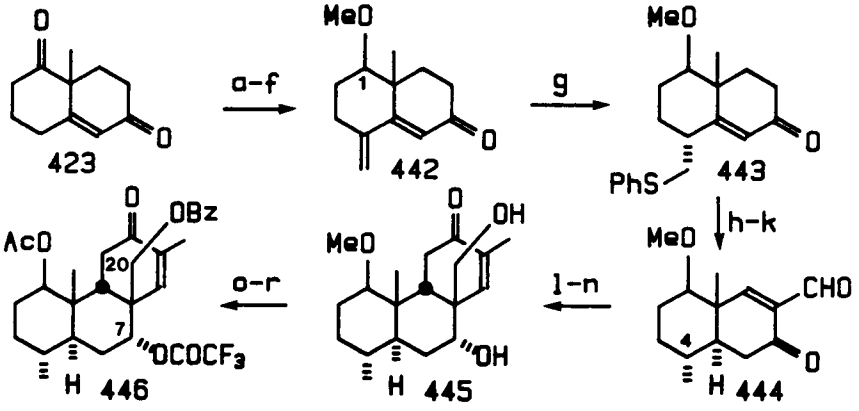


a) $BF_3 \cdot Et_2O$ b) PCC c) LDA or $LiN(TMS)_2$ followed by MoOPh, Davis' reagent or dibenzyl peroxydicarbonate

advanced intermediate 439 that still possessed the protected C-8 hydroxymethyl group led to the diketone 440, but the attempted MoOPh oxidation (as well as related efforts) also failed to provide the desired bis(α-ketol) 441.

We subsequently recast the synthesis in favor of intermediates that incorporated the C-4 methyl group early in the route and intermediates that permitted C-11 oxidation using manganese(III) acetate.[68] The need for various oxidations and reductions leading up to the tricyclic enone 446 in Scheme 68

Scheme 68



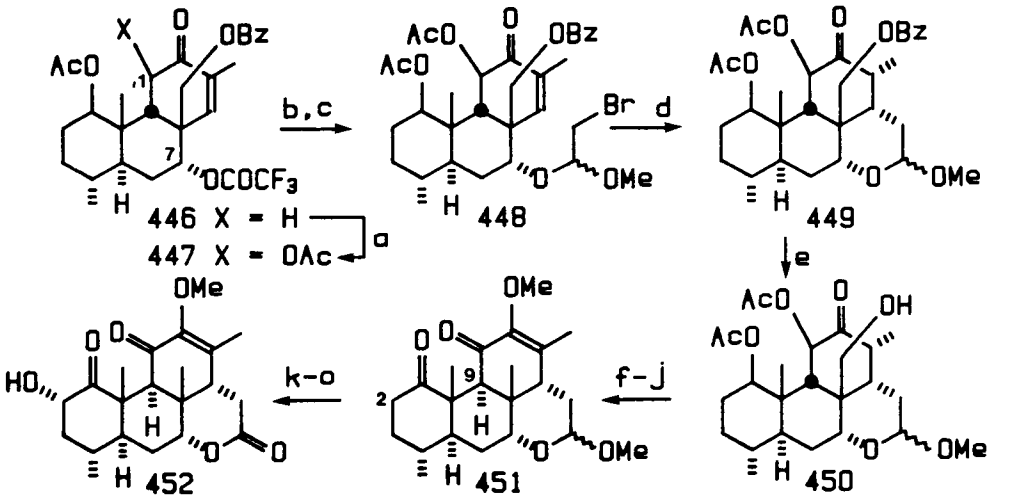
a) $NaBH_4$ (95%) b) NaH, MeI (89%) c) TMSCl, Et_3N (94%) d) $[CH_2=N(CH_3)_2]I$ (85%) e) CH_3I f) 20% NaOH, EtOAc (85% for e,f) g) PhSH, K_2CO_3 (85%) h) Li, NH_3 i) PCC (72% for h,i) j) NaH, HCO_2Et (98%) k) PhSeCl followed by H_2O_2 (93%) l) $CH_2=C(OTMS)C(CH_3)=CHOMe$ m) Red-Al n) H_3O+ (80% for l,m,n) o) PhCOCl, Py, DMAP (97%) p) TFAA, Py (88%) q) TMSCl, NaI, CH_3CN (92%) r) Ac_2O, Py (84%)

demanded the selection of the C-1β methoxy protecting group rather than the tert-butyldimethylsilyl ether protecting group used earlier. Preparation of the dienone 442 in combination

with a reductive desulfurization of the thiophenoxy-substituted enone 443 led ultimately to the bicyclic dienophile 444 having the correct C-4α methyl group and the AB trans-fused stereochemistry. The Diels Alder reaction of 444 with 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene provided, following reduction and hydrolysis, the tricyclic diol 445 in excellent yield. Protection of the C-20 alcohol as the benzoate and the C-7α alcohol as the trifluoroacetate ester set the stage for the deprotection of the C-1β methoxy group and acetylation to furnish the enone 446.

As shown in Scheme 69, the manganese(III) acetate oxida-

Scheme 69



a) $Mn(OAc)_3$, benzene (89%) b) $(NH_2)_2C=S$, $NaHCO_3$, EtOH (95%) c) $PhNMe_2$, $BrCH_2CH(OMe)Br$ (90%) d) $n\text{-}Bu_3SnH$ (70%) e) K_2CO_3, MeOH, 0°C (52%) f) PhOC(=S)Cl, Py (78%) g) $n\text{-}Bu_3SnH$ (69%) h) K_2CO_3, MeOH, 25°C (51%) i) Swern oxidation (63%) j) NaH, MeI (97%) k) 60% aq. HOAc l) Ag_2CO_3, Celite (59% for k,l) m) $CuBr_2$, MeOH (44%) n) Me_4NOAc (49%) o) K_2CO_3, MeOH, 25°C (76%)

tion of 446 that secured the C-1β,11β diacetate 447 in which we assumed that the acetate was introduced on the less hin-

dered exo-face of the tricylic system. Selective saponification of the C-7α trifluoroacetate in 447 and conversion to the α-bromoacetal 448 permitted the closure of the D ring using a free-radical cyclization to afford the protected δ-lactol 449. Selective saponification of the C-20 benzoate, reduction of the C-8β hydroxymethyl group to a C-8β angular methyl group, further saponification, Swern oxidation, and methylation provided the O-methyldiosphenol 451 in which the correct C-9α stereochemistry emerged for the first time. We completed the first enantioselective total synthesis of (+)-picrasin B (452) through a sequence involving hydrolysis and oxidation of the protected δ-lactol to the δ-lactone, bromination at C-2, acetolysis and hydrolysis. Current efforts are now focused on the manipulation of the δ-lactol 449 in order to gain access to quassinoids in the pentacyclic series.

IV. SUMMARY

The quassinoids have provided a fertile ground for the the development of new reagents or procedures and the further definition of newly discovered or well established reactions. Among the ever growing number of new procedures in the literature, the few that are most likely to prove useful will frequently appear in total syntheses where the test of functional group compatibility and stereoselectivity are extreme. The quassinoid syntheses illustrate this notion with the appearance of free radical cyclizations (Schemes 66 and 69), reductive decyanations (Scheme 22), palladium(II)-catalyzed oxidations of trimethylsilyl enol ethers (Scheme 21), sodium

hydrotelluride reductions (Schemes 55 and 57), and high pressure reactions (Schemes 28 and 44).

New procedures were often developed in response to specific structural features in the quassinoids. For example, the frequent appearance of diosphenol functionality in the quassinoids led to the development of procedures for the conversion of α-ketols to O-methyldiosphenols (Scheme 18) or the conversion of α'-hydroxyenones to diosphenols (Scheme 41). Solutions to the problem of introducing the oxymethylene bridge characteristic of the E ring include the rearrangement of tetrahydropyrans to tetrahydrofurans (Scheme 44), a thermal reaction of α-bromoketones with a proximal methoxymethyl ether (Schemes 45 and 46), application of Nicolau's selenocyclization procedure[54] (Schemes 29 and 48), ring opening of epoxides (Schemes 55 and 61), and the displacement of a neopentyl mesylate by a cyanohydrin (Scheme 40). Among the approaches to the δ-lactone characteristic of the quassinoids are an S_N2 inversion of a C-7β mesylate (Schemes 57 and 61), an iodotrimethylsilane-mediated cyclizations of α-iodoacetates to enones (Schemes 50 and 53), the chromium(VI)-catalyzed solvolysis of an allylic alcohol leading to a δ-lactone (Scheme 28), and the ring expansion of a γ-lactone (Scheme 39) or cyclopentanone (Schemes 16 and 23).

The application of traditional reactions in the quassinoid framework has further defined the scope of these reactions with regard to compatible substitution patterns and proximal functionality. Among these contributions, the following reactions stand out: Ganem's application of a Michael addition to

create selectively an acyclic stereocenter at C-9 (Scheme 47); Ziegler's application of the Claisen rearrangement to control acyclic stereochemistry at C-8 and C-14 as well as the application of an "ene" reaction to close ring C (Scheme 61); Takahashi's application[67] of a Robinson annelation to introduce the C ring in a heavily substituted cyclohexanone (Scheme 54); Fuch's application of the Nagata hydrocyanation reaction to introduce a functionalized C-8 angular methyl group (Scheme 40); Kametani's use of the Eschenmoser fragmentation to set the stage for the elaboration of ring A (Scheme 24); and Graf's and Takahashi's[44] application of the Wharton rearrangement to introduce functionality at the C-1 position. No single reaction has probably been more frequently used in the synthesis of quassinoids than the Diels-Alder reaction. Successful examples include intermolecular routes for introducing the B ring (Schemes 15) and the C ring (Schemes 18, 29, 32, 33, 35, 50 and 68), intramolecular variants for introducing the CD (Scheme 25) and BC rings (Schemes 22, 23, 56, 57, and 64), and recently the "aqueous" Diels-Alder process. It seems likely that future synthetic efforts in the quassinoid arena will contribute additional valuable methodology to organic chemistry.

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