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STRATEGIES AND TACTICS FOR THE SYNTHESIS OF OXYGENATED NATURAL PRODUCTS[1]

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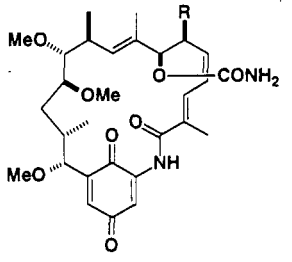
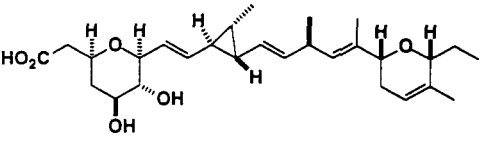
ABSTRACT.—The total synthesis of the ansa antibiotic macbecin I [**1**] is described exploiting an approach that features the oxidative transformation of furans into hydropyrans that then serve as conformationally biased templates for stereoselective refunctionalization and elaboration. A novel variant of the Mitsunobu reaction was developed that may be applied to the inversion of hindered secondary alcohols. In work directed toward the total synthesis of the antifungal antibiotic ambruticin [**3**], new and general methods have been invented for the asymmetric synthesis of functionalized cyclopropanes by intramolecular cyclopropanations of ω-unsaturated diazoacetates and the convergent stereoselective synthesis of trisubstituted alkenes.

One of the major challenges in contemporary organic chemistry lies in the development of efficient and concise routes to complex natural products. Such targets provide an important venue for the design and application of new strategies for constructing the rings, and appendages, and functional arrays that form the substituted framework of the molecule of interest. The emphasis on reducing the length of routes to natural products places a significant burden on the chemist to be as innovative as possible with respect to formulation of the synthetic plan. Toward this end, the efficiency of bond constructions and functional group interconversions must be maximized; starting materials, reagents and chemical reactions must be judiciously selected. The problems that arise during the course of the synthesis of functionally and stereochemically complex molecules should inspire the invention of new methods and reactions that have broad applicability. The art of natural product synthesis has matured to the point that it is not now so much a question of whether a molecule may be made, but what can be learned and what new chemistry can be developed by the undertaking. Thus, natural products should serve as targets of opportunity for the discovery of new and interesting chemistry.

We have been interested in the synthesis of a number of highly oxygenated natural products as a vehicle for developing general synthetic strategies and methods. For example, macbecin I [**1**] and herbimycin A [**2**], which differ only in the nature of the sub-



1 R=Me
2 R=OMe



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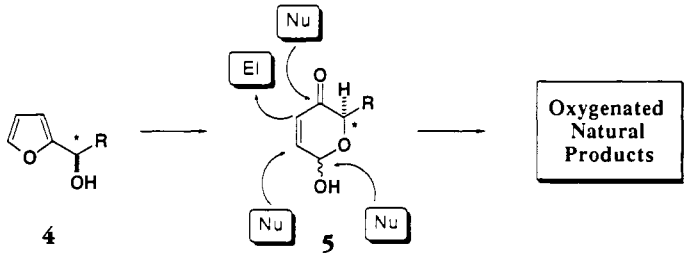
[1]Presented as a plenary lecture at the "Contemporary Natural Products Research" Symposium of the International Research Congress on Natural Products and 32nd Annual Meeting of the American Society of Pharmacognosy, Chicago, Illinois, July 21–26, 1991.

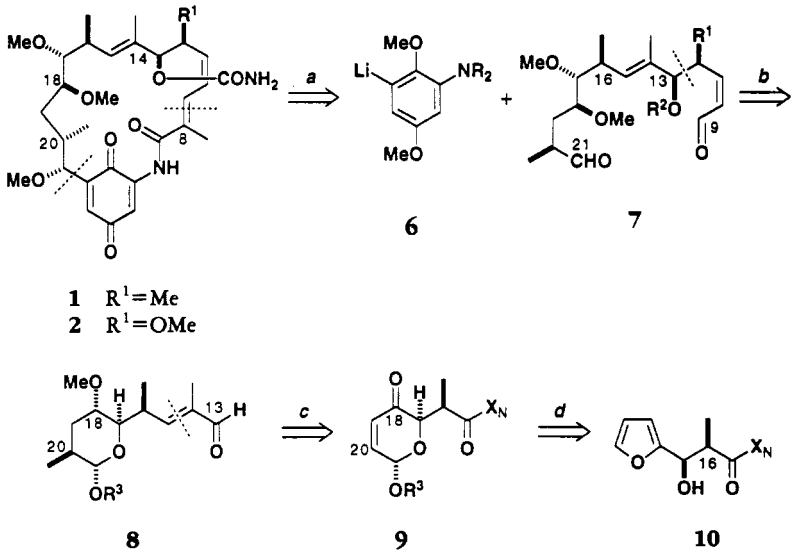
stituent R at C-12, are two representative members of the ansamycin family of antibiotics (1–8). These macrocyclic lactams exhibit a broad range of biological activities that include antibacterial, antifungal, herbicidal, antiviral, and antitumor. Owing to their biological activity and structural complexity, **1** and **2** have been targets of a number of synthetic investigations, and these efforts have recently culminated in the total syntheses of macbecin I [**1**] (9–13) and herbimycin A [**2**] (14). Another molecule of current interest is ambruticin [**3**], a unique, orally active antifungal agent that exhibits in vitro and in vivo activity against a variety of pathogenic fungi (15–17). Significantly, **3** is effective against *Histoplasma capsulatum* and *Coccidioides immitis*, which have been best treated previously with the highly toxic agent amphotericin B. There have been several preliminary studies directed toward the synthesis of **3** (18–20) and its total synthesis was recently recorded (21).

We have been interested in exploiting the furan-hydropyranone oxidative transform **4**↦**5** as a key step in formulating the strategy that is depicted in general terms in Scheme 1 for the asymmetric syntheses of oxygenated natural products such as **1**–**3** (22–25). One attractive feature of this plan is that the key intermediate hydropyranones **5** are endowed with useful functionality so that the reactions of derivatives of **5** with various nucleophiles and electrophiles provide an avenue for the introduction of new substituents and functionality as shown. The stereochemical course of these operations is directed in a predictable fashion by the stereogenic center C* of the conformationally biased hydropyran. This center may be established at an early stage by the asymmetric synthesis of the furfuryl carbinol **4** by one of a variety of established methods.



SCHEME 1

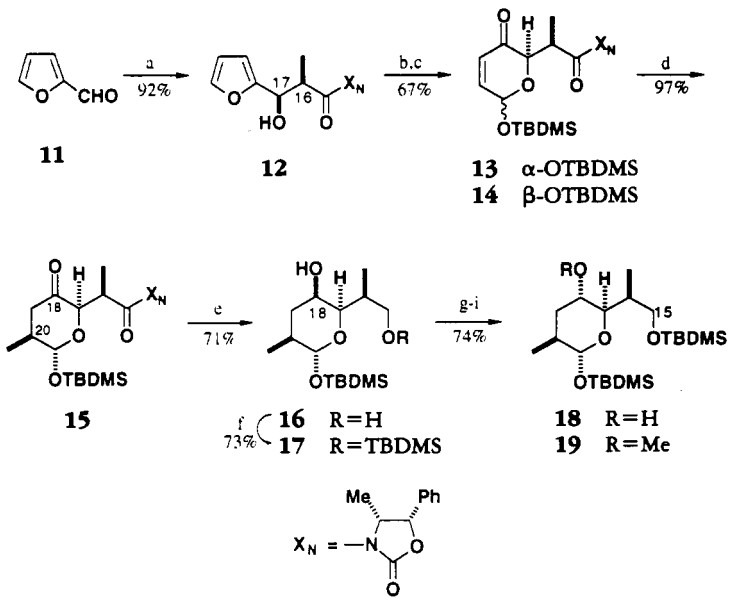
ASYMMETRIC SYNTHESIS OF MACBECIN I.—One of the characteristic structural features of the ansamycins macbecin I [**1**] and herbimycin [**2**] is a nineteen-membered ring lactam in which the ansa tether bridges the meta positions on a substituted benzoquinone moiety. Thus, the development of techniques for effecting the macrocyclizations of highly functionalized substrates could be one potential area for ancillary research. The construction of the ansa chain itself poses numerous stereochemical challenges, since it contains seven stereogenic centers, an isolated trisubstituted double bond, and a (*Z,E*)-diene. Following the general strategy illustrated in Scheme 1, we devised several approaches to **1** and **2**, one of which is the linear approach outlined in retrosynthetic format in Scheme 2. The pairwise disconnections shown in *a* afford the aromatic subunit **6** and the fragment of the ansa chain **7**, the latter being the key synthetic subgoal. We envisioned that **7** could be derived from the hydropyran **8**, which might be exploited as an advanced synthetic precursor for both macbecin I [**1**] and herbimycin A [**2**]. The derivation of **8** from **9** exploits the use of the hydropyran ring of **9** as a conformationally biased template for the elaboration of the two stereocenters at C-18 and C-20. The intermediacy of **9** from **10** follows from the general strategy in



SCHEME 2

Scheme 1. We have recently implemented this plan and completed the asymmetric synthesis of **1** (13); some of the details of this effort are recorded below.

The absolute stereochemistry at C-16 and C-17 of the ansa chain of macbecin I was set in the opening move of the synthesis by the Evans' asymmetric aldol reaction (26) of furaldehyde [**11**] to give **12** (Scheme 3). Oxidative processing of the furan ring fol-



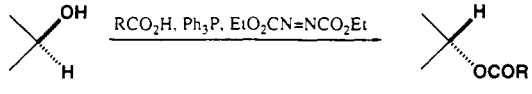
(a) EtCO-X_N, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0°. (b) Br_2, MeCN-H_2O, −20°. (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, −78°. (d) Me_2CuLi, TMSCl, THF, −78°; H_3O^+. (e) $NaBH_4$, −20°; DIBAL-H, 0°. (f) TBDMS-Cl, NEt_3, DMAP, CH_2Cl_2, room temperature. (g) 4-$O_2NC_6H_4CO_2H$, Ph_3P, DEAD, PhH, room temperature. (h) NaOH, MeOH, room temperature. (i) KH, MeI, THF, 0°.

SCHEME 3

lowed by protection of the anomeric hydroxyl function as its tert-butyldimethylsilyl ether gave a chromatographically separable mixture (3:1) of α- and β-anomers **13** and **14**, respectively. The undesired β-anomer **14** was recycled by sequential deprotection and protection to give **13** in 67% overall yield from **12** after two recycles. Although conjugate addition of lithium dimethylcuprate to enone **14** was not highly stereoselective under standard conditions, the reaction proceeded to give **15** as the exclusive product when conducted in the presence of chlorotrimethylsilane (27).

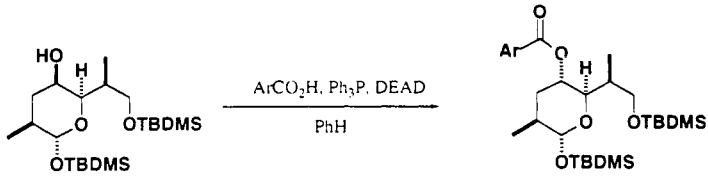
At this stage it was necessary to convert the carbonyl group at C-18 into a methyl ether via reduction and subsequent methylation. Unfortunately, stereoselective reduction of the C-18 ketone function to give the requisite equatorial alcohol proved problematic. Reduction of **15** under a wide range of reaction conditions using various hydride sources as well as equilibrating reduction protocols invariably produced a preponderance of the unwanted axial stereoisomer. Thus, the axial methyl substituent at C-20 plays a major role in dictating the facial selectivity in this reduction, even in those cases where reduction was conducted under equilibrating conditions. We therefore opted for a stepwise procedure that commenced with hydride reduction of the C-18 ketone in **15**; this reaction proceeded stereoselectively from the equatorial face with concomitant cyclization and loss of the chiral auxiliary to give an intermediate γ-lactone that was further reduced to furnish the diol **16**. Inversion of the stereogenic center at C-18 of **17** to give **19** could be achieved, albeit in modest yield, by a sequence of reactions involving displacement of the corresponding mesylate with cesium propionate followed by hydrolysis and *O*-methylation. Although this stepwise protocol was successful, we sought to develop a more expedient solution to this problem, and we examined the Mitsunobu reaction as a possible alternative.

The Mitsunobu reaction (28) is a useful and commonly employed method for inverting the stereochemistry of alcohols under mild conditions according to Scheme 4. While the efficacy of this procedure is well documented for a variety of substrates and nucleophiles, the reaction is sensitive to the steric environment of the alcohol, and



SCHEME 4

Mitsunobu inversions of hindered alcohols may be problematic. For example, subjection of **17** to the standard Mitsunobu reaction conditions using benzoic acid as the nucleophile in the presence of triphenylphosphine and diethylazodicarboxylate in tetrahydrofuran returned only starting material. Although the use of C_6H_6 as a solvent has been reported to provide improved results with some substrates (29), substitution of C_6H_6 for THF in the present instance led to the formation of the desired product **20** (Ar = Ph) in only 27% yield (Scheme 5). However, we discovered that when the Mit-



17 **20**

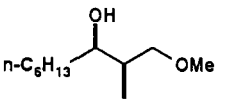
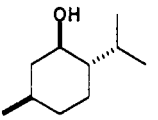
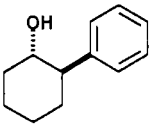
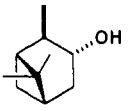
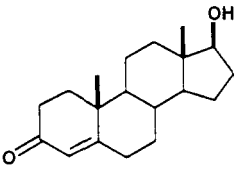
SCHEME 5

sunobu reaction of **17** was executed using *p*-nitrobenzoic as the nucleophile, **20** (Ar = *p*-$O_2NC_6H_4$-) was obtained in 86% yield; hydrolysis of **20** then gave **18** in excellent overall yield from **17**.

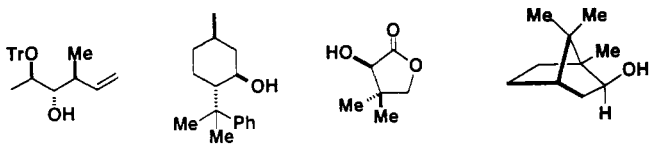
In subsequent studies, we found that this variant of the Mitsunobu reaction may be more generally exploited to effect the stereochemical inversion of a number of hindered secondary alcohols (30). Examination of the selected results summarized in Table 1 reveals that this new protocol is particularly effective for secondary alcohols bearing substituents on one of the carbon atoms adjacent to the carbinol carbon, and in most cases dramatically improved yields of inverted product were obtained. However, extension of the methodology to more sterically congested alcohols sometimes resulted in diminished reactivity and low yields. For example, substrates such as **21**, in which the alcohol moiety is flanked by two branched substituents, gave none of the desired product, even under forcing reaction conditions (excess reagent, prolonged reaction times, and/or heating). Little or no reactivity was observed for alcohols with relatively large α substituents (e.g., **22–24**). Interestingly, use of aromatic carboxylic acids with electron-releasing rather than electron-withdrawing substituents as the nucleophile, such as is exemplified in the case of *p*-methoxybenzoic acid (entry 2), resulted in poor yields of hydroxyl inversion. Thus, we have shown that in a number of instances the yields in Mitsunobu reactions of hindered alcohols may be significantly improved by substituting *p*-nitrobenzoic acid for benzoic acid.

Returning to the task posed by the synthesis of macbecin I, it was then necessary to begin the chain extension of the ansa subunit **19**. In the event, selective deprotection of

TABLE 1. Mitsunobu Inversions of Secondary Alcohols Using Aryl Carboxylic Acids.

Entry	Alcohol	$ArCO_2H$	Conditions[a]	Yield (%)
1		*p*-$O_2NC_6H_4CO_2H$ $PhCO_2H$	7.0 equiv, room temperature, 17 h	73 19
2		*p*-$O_2NC_6H_4CO_2H$ $PhCO_2H$ *p*-$MeOC_6H_4CO_2H$	1.2 equiv, room temperature, 1 h	84 27 17
3		*p*-$O_2NC_6H_4CO_2H$ $PhCO_2H$	1.5 equiv, room temperature, 6 h	99 58
4		*p*-$O_2NC_6H_4CO_2H$ $PhCO_2H$	1.2 equiv, room temperature, 1 h	50 35
5		*p*-$O_2NC_6H_4CO_2H$ $PhCO_2H$	1.2 equiv, 81°, 20 min	89 62

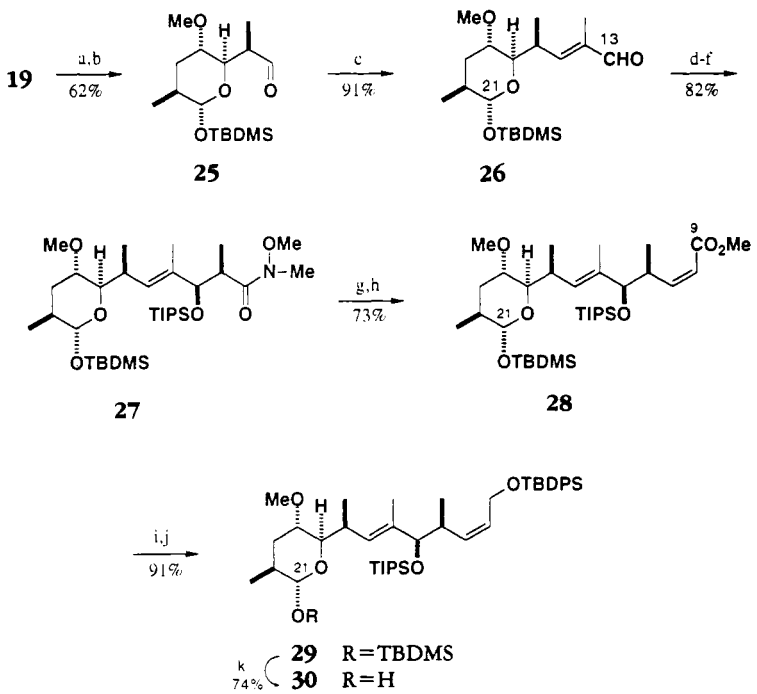
[a]Number of equiv. refers to the stoichiometry of Ph_3P, $ArCO_2H$, DEAD with respect to the substrate (optimized for *p*-nitrobenzoic acid). All reactions were conducted in C_6H_6.



21 22 23 24

the primary hydroxyl group at C-15 of **19** followed by oxidation of the alcohol using the Parikh protocol (31) provided the aldehyde **25** (Scheme 6). The highly stereoselective conversion of **25** into **26** was implemented via a Peterson olefination using the anion derived from (2-triethylsilyl)propionyl-*N*-cyclohexylimine followed by acid-catalyzed isomerization of the intermediate unsaturated imine prior to its hydrolysis (32).

With the unsaturated aldehyde **26** in hand, it would be possible to pursue either macbecin I [**1**] or herbimycin A [**2**] as the synthetic target, but the former was selected as our initial objective. When **26** was subjected to an Evans' aldol reaction, an intermediate adduct was obtained that was transformed into the protected hydroxamate (33) **27** in 82% overall yield. Reduction of the hydroxamate function followed by stereoselective *Z*-olefination (34) then gave **28**, which possesses the C-9–C-21 segment



(a) CF_3CO_2H/H_2O (9:1), THF, 0°. (b) Pyridine/SO_3, NEt_3, DMSO, room temperture (c) (2-triethylsilyl)propionyl-*N*-cyclohexylimine, *sec*-BuLi, THF −78 to −30°; CF_3CO_2H, 0°; H_2O. (d) EtCO-X_N, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0°. (e) $MeONMeH_2Cl$, $AlMe_3$, CH_2Cl_2, −40 to −10°. (f) TIPS-OTf, 2,6-lutidine, CH_2Cl_2, 0°; (g) DIBAL-H, THF, −78 to −50°; (h) KHMDS, 18-C-6, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, −78 to −40°. (i) DIBAL-H, THF, −20°. (j) TBDPS-Cl, DMAP, CH_2Cl_2, room temperature. (k) 1.5 M aqueous HF, MeCN, THF, room temperature.

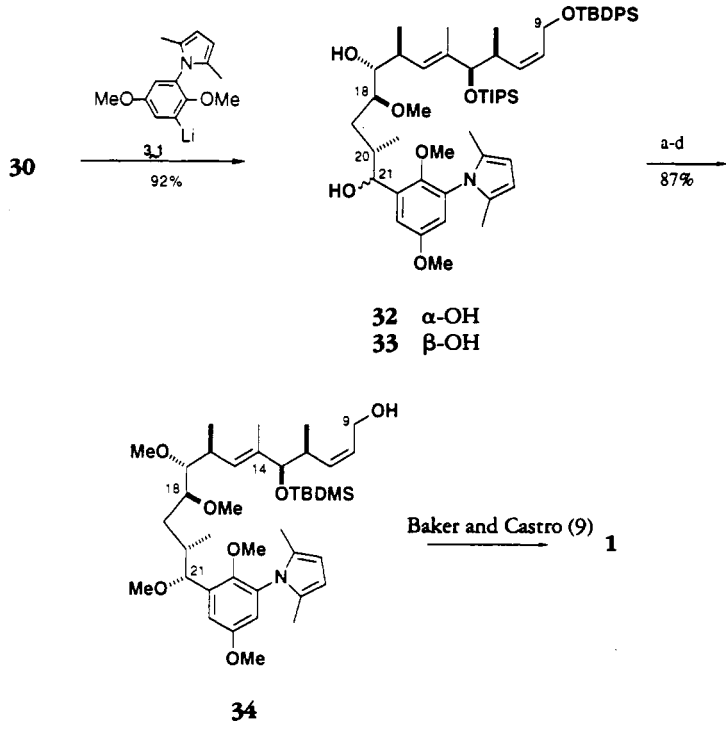
SCHEME 6

of the ansa chain of macbecin I. In order to set the stage for the addition of the aryl subunit, **28** was first converted into **29** in a straightforward fashion. Selective removal of the TBDMS protecting group from the anomeric center of **28** was then achieved using aqueous HF in MeCN/THF to give the lactol **30**.

The aryl subunit of macbecin I was then appended by treating **30** with a threefold excess of the aryllithium reagent **31** (35) to deliver a readily separable mixture (3.5:1) of the adducts **23** and **24** in 92% combined yield (Scheme 7). It is noteworthy that **31** added to the C-21 aldehyde function of **30** predominantly via the desired Felkin-Anh (Cram) mode in contrast to that observed in a related addition reported by Coutts *et al.* (10). The structure of **32** was unequivocally established by its conversion in 87% overall yield into **34**, which was identical (^{1}H and ^{13}C nmr) with an authentic sample provided by Dr. Raymond Baker.

Since **34** was an advanced intermediate in Baker's asymmetric synthesis of macbecin I [**1**] (9), its preparation by the route outlined above constitutes a synthesis of **1** in a formal sense. However, we are presently exploring more direct methods for converting **32** and related compounds into macbecin I. Moreover, we are examining several strategies for completing more highly convergent syntheses of both macbecin I and herbimycin A from the key intermediate **25**.

SYNTHETIC STUDIES DIRECTED TOWARD AMBRUTICIN [**3**].—The retrosynthetic analysis of our approach to ambruticin [**3**] features three straightforward double bond disconnections to give the four subunits **35–38** as outlined in Scheme 8. We envisioned that the hydropyrans **35** and **38** should be accessible from the corresponding



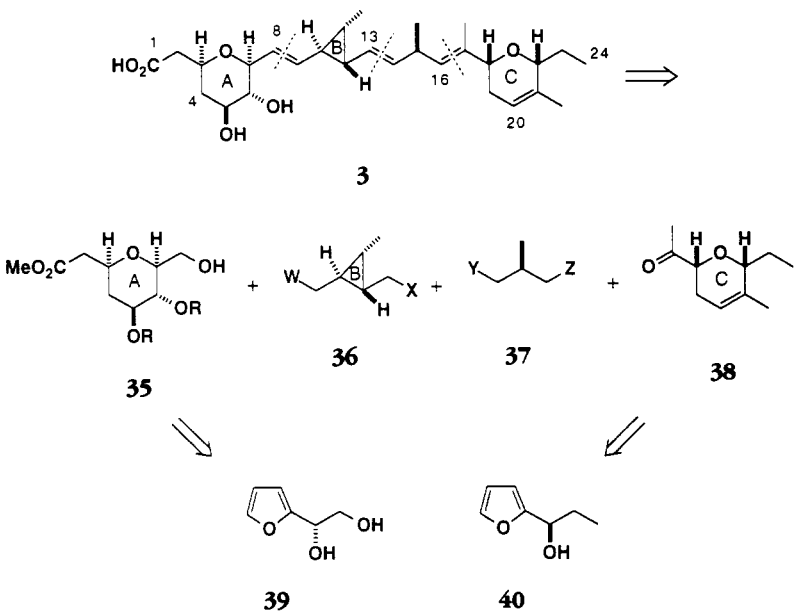
(a) KH, THF, MeI, 0°. (b) TBAF, THF. (c) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2. (d) TFA, aqueous THF.

SCHEME 7

furans **39** and **40** according to the plan outlined in Scheme 1. Since we had developed considerable expertise in elaborating furans into substituted hydropyrans, our concerns in the initial stages of efforts directed toward ambruticin have been in solving problems in two ancillary areas. At the outset of our studies there were no general methods for achieving the asymmetric synthesis of trisubstituted cyclopropanes related to **36**; it would be necessary to address this problem. Moreover, although the stereoselective synthesis of disubstituted alkenes by convergent tactics such as the Julia coupling are well documented, corresponding connective methods for the efficient, stereoselective synthesis of trisubstituted alkenes by coupling two large fragments were unavailable when we began our work. Thus, the synthetic approach that we set forth for the preparation of **3** offered a unique opportunity to develop new methods for the asymmetric synthesis of 1,2,3-trisubstituted cyclopropanes and the convergent, stereoselective synthesis of trisubstituted alkenes.

Catalytic asymmetric synthesis of cyclopropanes.—Cyclopropanes are integral substructures of a number of natural products, as is nicely exemplified by the target ambruticin. The importance of cyclopropanes is further enhanced by their ability to serve as mechanistic (36–38) and biological (39–41) probes as well as synthetic intermediates (42,43). Although numerous methods for the stereoselective synthesis of cyclopropanes exist (44–46), only recently have there been reports of general techniques for their asymmetric synthesis (47–65). In connection with our synthetic efforts directed toward ambruticin coupled with our interest in exploiting trisubstituted cyclopropanes as rigid replacements of peptide secondary structure (39–41), we embarked several years ago on a program to develop novel and efficient methods for the asymmetric synthesis of 1,2,3-trisubstituted cyclopropanes.

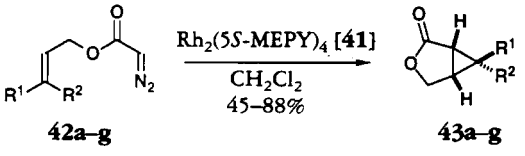
Although the metal-catalyzed decomposition of diazo carbonyl compounds in the presence of alkenes to give cyclopropanes is well known, there are relatively few reports of the use of chiral catalysts to obtain high levels of enantioselectivity in these transformations. Of particular merit in such intermolecular cyclopropanations are the chiral salicylaldimine copper (II) catalysts described by Aratani (58), the chiral (semicor-



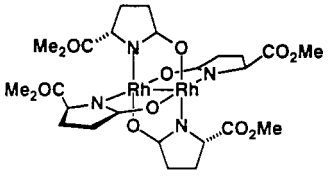
SCHEME 8

rinato) copper (II) catalysts designed by Pfaltz and co-workers (59–61) and their bis-oxazoline analogues reported by Masamune and co-workers (62,63) and Evans and co-workers (64,65); however, none of these catalysts had been applied to intramolecular cyclopropanations. In order to address this need, we began a search for catalysts that could induce highly enantioselective cyclizations of ω-unsaturated diazoacetates.

A common tactic in the design of catalysts that induce enantioselective carbenoid transformations has historically consisted of attaching chiral ligands to a central metal atom. To this end, we prepared a series of dirhodium (II) amide complexes by ligand substitution using a variety of chiral amide ligands. Eventually we discovered that dirhodium (II) tetrakis[methyl 2-pyrrolidone-5-(*S*)-carboxylate] Rh_2(5*S*-MEPY)$_4$ [**41**], which was prepared by simply heating rhodium (II) acetate with 5-(*S*)-methyl pyroglutamate, catalyzed the intramolecular cyclopropanation of allylic diazoacetates with extraordinary enantioselectivity, and some of these results are summarized in Scheme 9 (47). The requisite starting materials **42a–g** were prepared by reaction of the corresponding allylic alcohol with glyoxylic acid chloride *p*-toluenesulfonylhydrazone (66) or by sequential diketene condensation, diazo transfer, and deacylation (47). The cyclizations were simply executed by slow addition of **42a–g** to a solution of Rh_2 (5*S*-MEPY)$_4$ [**41**] (1.0 mol %) in anhydrous CH_2Cl_2 to give the lactones **43a–g** with very good to excellent enantioselectivities (70↦≥94%). The absolute configuration of the lactones **43a–g** was assigned based upon comparison of the signs of rotation of the known cyclopropyl lactones **43a** and **43b**; further support for these assignments was obtained by establishing the structure of the (−)-methyl ester of a derivative of lactone **43c** by single crystal X-ray analysis (67). In general, the intramolecular cyclopropanations of (*Z*)-olefins proceeded with greater levels of enantioselectivity than the corresponding (*E*)-isomers. Significantly, the enantiomeric catalyst Rh_2 (5*R*-MEPY)$_4$ is also readily available and may be employed to induce the intramolecular carbene additions of **42a–g** to give the enantiomers of **43a–g**. The cyclopropyl lactones **43a–g** have been used as key intermediates in the preparation of biologically active peptide mimics that are conformationally constrained in a rigid β-strand array (40,41).



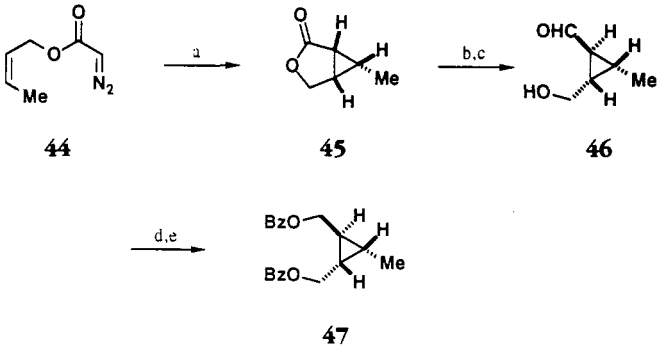
42a–g **43a–g**



41

Series **a** $R^1=R^2=H$
b $R^1=R^2=Me$
c $R^1=H$, $R^2=Ph$
d $R^1=Ph$, $R^2=H$
e $R^1=H$, $R^2=Bn$
f $R^1=H$, $R^2=i$-Bu
g $R^1=H$, $R^2=(n\text{-Bu})_3Sn$

SCHEME 9



44 **45** **46**

47

(a) $Rh_2(5S\text{-MEPY})_4$, CH_2Cl_2, Δ. (b) DIBAL-H, THF, −90°. (c) LiOMe, MeOH, Δ. (d) DIBAL-H, THF, 0°. (e) BzCl, Pyridine, DMAP, room temperature.

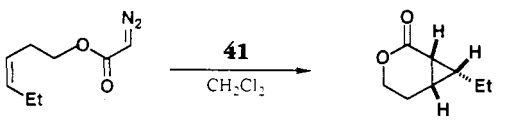
SCHEME 10

Application of this general procedure to the problem of asymmetric synthesis of a synthetic equivalent of the cyclopropane fragment **36** was then undertaken (Scheme 10). The $Rh_2(5S\text{-MEPY})_4$-catalyzed cyclization of **44** proceeded smoothly to give the bicyclic lactone **45** in 92% enantiomeric excess. Subsequent refunctionalization of **45** gave **47** having an optical rotation virtually identical to that reported by Just and Potvin (68). The conversion of **45** into **46** proceeded in low yield, and improved tactics must be developed for the elaboration of **45** into a cyclopropane derivative that may be more effectively used as an intermediate in the total synthesis of ambruticin.

We have recently initiated a number of exploratory experiments directed toward expanding the utility of **41** as a catalyst to effect asymmetric intramolecular cyclopropanations. In one such study, we discovered that **41** induces the cyclization of homoallylic diazoesters in enantiomeric excesses ranging from 71 to 90% as illustrated by the cyclization of **48** to give **49** (Scheme 11). The absolute sense of asymmetric induction in these reactions appears to be identical to that observed for the cyclization of the allylic diazoacetates as determined by the single X-ray analysis of the (*R*)-(+)-α-methylbenzylamide derivative of **49**.

As evidenced by the foregoing discussion, the rhodium (II) catalyst **41** may be exploited for the asymmetric synthesis of substituted cyclopropanes bearing a variety of substitution patterns. Since the mirror image of **41** is also readily available, both enantiomers of a cyclopropyl lactone may be efficiently prepared with high enantioselectivity from a single ω-unsaturated diazoester. Further studies are in progress to determine precisely the scope and limitations of these catalysts to effect enantioselective cyclizations of other unsaturated systems and to discover new catalysts that may be even more efficient.

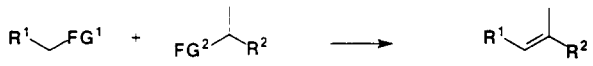
Stereoselective synthesis of trisubstituted alkenes.—A common functional element present in a large number of natural products is a trisubstituted carbon-carbon double bond.



48 **49**

SCHEME 11

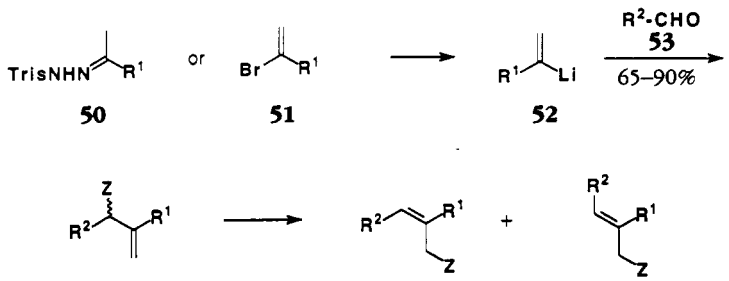
Consequently, the convergent and stereoselective construction of trisubstituted alkenes constitutes an important problem in modern synthetic organic chemistry (69,70). In the context of our work directed toward the synthesis of ambruticin [**3**] and other natural products, we became aware of the paucity of known methods that could be employed for coupling two fragments with the stereoselective formation of a trisubstituted double bond according to Scheme 12 (71–73). We therefore set to the task of devising solutions to this problem.



SCHEME 12

After considering a number of possible connective routes to alkenes, we formulated the sequence of reactions outlined in Scheme 13. The approach features coupling of the two requisite fragments by nucleophilic addition of a vinyl anion **52**, which are prepared either from the trisylhydrazone **50** or the vinyl bromide **51**, to an aldehyde **53** to give a mixture of epimeric allylic alcohols **54**. Following conversion of **54** into the respective xanthates **55**, facile [3,3]-sigmatropic rearrangement provides the corresponding dithiocarbonates as a mixture of geometric isomers **56** and **57**. Subsequent scission of the carbon-sulfur bond of **56** and **57** by a tributylstannyl radical furnishes an intermediate allyl radical that rapidly equilibrates to the more stable transoid form followed by reaction with a hydrogen atom source to deliver **58** as the major product (74–76). This procedure has recently been applied to the stereoselective synthesis of a number of trisubstituted alkenes, and several selected examples are summarized in Table 2 (77). The conversion of **53** into the mixture of **58** and the minor isomeric components **59** and **60** may be conducted in only two operations in optimized cases; thus, although there are a number of individual steps, the entire sequence may be readily executed in two pots.

The [3,3]-sigmatropic rearrangement of the allylic xanthates **55** appears in each case to give the allylic dithiocarbonates **57** as the major products, although the preference is not strong. This trend is qualitatively in accord with the rearrangement of **55** via the more stable chair-like transition state. Since the major products obtained upon radical hydride reduction of the mixtures of **56** and **57** were the desired (*E*)-alkenes **58**, there is no meaningful correlation between the stereochemistry of the intermediate allylic dithiocarbonates **56** and **57** with the stereochemical outcome of the radical reduc-



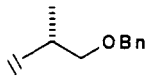
54 Z=OH
55 Z=OCS_2Me
60 Z=H

56 Z=SCOSMe
58 Z=H

57 Z=SCOSMe
59 Z=H

SCHEME 13

TABLE 2. Convergent Synthesis of Alkenes According to Scheme 13.

Entry	R^1	R^2	% overall yield of **56** and **57** (**56**:**57** ratio)	% overall yield of reduction (**58**:**59**:**60** ratio)
a	i-C_3H_7-	n-C_6H_{11}-	89 (5:1)	90 (11:1:6)
b	cyclo-C_6H_{11}-		95 (1.5:1)	89 (9.6:1.2:1)
c	cyclo-C_6H_{11}-		85 (1.4:1)	81 (20:1:1)
d	cyclo-C_6H_{11}-	C_6H_5-	93 (2.2:1)	94 (6.5:2:1)
e	C_6H_5-	i-C_3H_7-	87 (2.8:1)	84 (50:1:5)

tion. In control experiments, mixtures of **56** and **57** that differed in composition from those obtained directly from the rearrangement were subjected to the conditions of the radical reduction. Since the ratios of **56** and **57** did not change, we presume that no thermal isomerization about the double bond of **56** and **57** via reversible [3,3]-sigmatropic rearrangement occurred during the reduction. In another control experiment, we demonstrated that the product olefins **58** and **59** did not isomerize in the presence of tri-*n*-butyltin hydride and AIBN in refluxing C_6H_6. These preliminary observations suggest that (*Z*)↦(*E*) isomerization of the intermediate allyl radical that was generated upon reaction of **56** and **57** with tri-*n*-stannyl radical occurs prior to its reduction via hydrogen atom transfer. Other hydride donors were examined in the hope that enhanced stereoselectivity might be observed, but no improvement has yet been obtained.

This new procedure for the convergent synthesis of trisubstituted alkenes proceeds with significant levels of stereoselectivity to furnish the (*E*)-alkenes **58** as the major product. We are presently exploring other variants of this approach in an effort to develop more stereoselective and efficient procedures for effecting this important construction for eventual application to the synthesis of ambruticin and other natural products.

CONCLUDING REMARKS.—We have seen how the natural products macbecin I [**1**] and ambruticin [**3**] can truly be employed as targets of opportunity for the invention, development, and application of new synthetic strategies and methods. For example, the furan/hydropyran oxidative transform (Scheme 1) may be generally exploited to provide conformationally biased hydropyrans in optically pure form. This conversion was featured in a concise sequence of stereoselective reactions proceeding via the intermediates **11**↦**12**↦**15**↦**19**↦**30** and leading ultimately to **34**, which has been previously converted into macbecin I [**1**]. During the course of our work directed toward **1**, a novel variant of the Mitsunobu reaction was invented that may be generally used to effect the inversions of a number of sterically hindered alcohols. We have designed and developed new and useful procedures for inducing highly enantioselective intramolecular cyclopropanations; the intermediate cyclopropyl lactones may then be converted into a number of interesting compounds including the cyclopropane subunits in ambruticin [**3**] (i.e., **45** and **47**) and various peptide mimics. Finally, a new tactic for performing the convergent, stereoselective synthesis of trisubstituted alkenes was developed. Further extensions of various aspects of the work described herein are in progress, and the results of these investigations will be reported in due course.

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