ENANTIOTOPIC SYNTHESIS OF NATURAL PRODUCTS:
MERRILACTONE AND GUANACASTEPENE

Heedong Yun,1 Zhaoyang Meng,1 and Samuel J. Danishefsky1,2,*

1Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027 and 2Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Ave., New York, NY 10021 (USA)

Abstract – We have previously disclosed the total syntheses of racemic merrilactone A and guanacastepene A. We describe herein the development of new routes to key intermediates in the first-generation syntheses, which will allow us to access both merrilactone A and guanacastepene A in enantiomerically enriched form.

INTRODUCTION
There is a longstanding interactivity between the fields of natural product discovery, total synthesis, synthetic methodology, and the development of leads for drug discovery. The rich variety of structural motifs found in natural products serves to challenge the members of the synthetic community to devise programs for their total synthesis and to reduce these perceptions to practice. Often, it is the case that, in contemplating such designs, the chemist realizes that the methods available to the field are actually insufficient to encourage progression in a particular design. Clearly, the “plausibility” of a strategy is a direct function of the state of the methodology. Hence, in essence, the desire, focus, and sense of challenge, which the synthesis of natural products tends to provide, also provides encouragement for methodologists to explore new departures in total synthesis. These may enable formulation of new strategies.

Finally, it is becoming increasingly apparent, though the point had not been made in great detail earlier, that natural product structures provide highly suggestive initiation points in the development of new agents of medicinal value. It is often the case that, when medicinal agents are chiral in nature, one

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.
antipode will possess significant therapeutic activity, while the other will demonstrate no appreciable medicinal benefit, and may actually induce undesirable side effects in a clinical setting. Consequently, it is well appreciated in the synthetic community that the elevation of a natural product from a target of purely synthetic interest to a viable candidate for drug development is often predicated on the ability to access material in an enantiomerically controlled fashion. Thus, those synthetic chemists who aspire to influence the interface of total synthesis and drug discovery are charged with the task of developing synthetic solutions that allow for the selective formation of one antipode in preference to the other. It is not surprising, then, that there is a steadily growing field of organic methodology devoted to the development of methods to allow access to enantiomerically enriched synthetic products.

One can consider several general mechanisms through which to achieve enantiocontrol in total synthesis. Perhaps the most straightforward approach is to design the synthetic route such that one of the starting materials is a member of the chiral pool of readily available, naturally occurring compounds (cf. amino acids, carbohydrates). This solution, while undeniably appealing in its simplicity, may suffer from a lack of broad applicability to the total synthesis of varied and highly complex structural motifs. Alternatively, one might temporarily install a readily removable chiral auxiliary, which would dictate facial selectivity in a key stereodefining transformation. Upon cleavage of the auxiliary, the previous diastereo bias translates to enantio bias. This approach inevitably requires some concession in the overall efficiency of the synthetic route, since the chiral auxiliary must be installed and removed in the course of the synthesis. The burgeoning field of enantioselective catalysis seeks to address this shortcoming through the development of methods that rely on catalysts of defined chirality to exert stereofacial control in the transition states of stereodefining reactions. Enantioselective catalytic methods have been developed to introduce chirality to substrates lacking stereocenters and, less frequently, to effect the desymmetrization of meso compounds.

In this paper, which we are pleased to submit to honor the wonderful accomplishments of the late Professor Kenji Koga, we select two recent cases from our laboratories, which serve, very nicely, to underscore the relationship between methodology and strategy in the context of attempting to synthesize, in antipodally pure form, natural products of potential medicinal import. While these methods have been communicated earlier, we provide herein a more detailed insight into the discovery process.

**MERRILACTONE A**

Merrilactone A, isolated from the pericarps of the *Illicium merrillianum* plant, has been shown to promote *in vitro* neurite outgrowth in rat cortical neurons at concentrations as low as 0.1 µM. Because decreased neurotrophic support is a hallmark of neurodegenerative disease, it is hoped that neurotrophically active small molecules, such as merrilactone A, may prove to be useful clinical agents.
in the treatment of progressive neurological disorders. Our laboratory has an ongoing program devoted to the synthesis and biological evaluation of naturally occurring small molecule neurotrophic factors. As such, we have begun to assemble a small library of fully synthetic neurotrophins based on leads arising from natural products. These entries now include tricycloillicinone, jiadifenin, NGA0187, and scabronine G. In this context, we had been attracted earlier to merrilactone A, due to its intriguing biological profile, as well as its structural properties.

Our first objective - the preparation of racemic merrilactone A - was accomplished over 20 steps, in ca. 10% overall yield (Scheme 1). Briefly, the synthesis commenced with the Diels-Alder reaction of butadiene and 2,3-dimethylmaleic anhydride to afford cycloadduct. Reduction of the anhydride, as shown, afforded lactone which was converted to through an ozonolytic ring contraction sequence. Johnson orthoester Claisen rearrangement of provided a 1.8 to 1 diastereomeric mixture of the desired isomer and the undesired. Next, iodolactonization of provided 9, which was ultimately advanced to the vinyl bromide. A key feature of the synthesis was the free radical induced cyclization of, which proceeded in 90% yield to afford the densely functionalized tetracycle. Acid-mediated isomerization of the external olefin, with concomitant alcohol deprotection, afforded, which was converted to merrilactone A (1) through olefin epoxidation, followed by intramolecular epoxide opening.
Having accomplished the synthesis of racemic merrilactone A, we next sought to adapt the route to allow access to either antipode of the natural product. In our original route, it was the Diels-Alder reaction \((\text{cf. } 2 + 3 \rightarrow 4)\) that provided the first chiral intermediate of the synthesis. However, given the high temperatures required for the cycloaddition, we considered it unlikely that this transformation would be amenable to enantioselective catalysis. It seemed likely that in order to achieve our objective of accessing optically active merrilactone A, we would need to at least partially redesign our first-generation synthesis.

We selected iodolactone \((9)\) as the target compound for our modified synthetic route for several reasons. First, we consider the first-generation route from intermediate \((9)\) to merrilactone A to be particularly concise and efficient. Thus, if \(9\) were to be prepared in enantiomerically enriched form, its conversion to merrilactone A via the route developed for the racemic synthesis would be a foregone conclusion.

The first-generation synthesis of intermediate \((9)\) however, suffers from what we deemed to be two significant shortcomings. First, the reduction of anhydride \((4)\) to lactone \((5)\) is lacking in regioselectivity. Although the two products obtained from the reduction can be manipulated to converge upon the same lactone \((5)\), this solution, albeit high-yielding, has proven to be somewhat cumbersome. Of perhaps greater concern is the lack of stereoselectivity observed in the Claisen rearrangement of compound \((6)\) (ratio of products \(7:8 = 1.8:1)\). Despite considerable efforts at optimization, we were unable to gain additional bias in favor of the desired stereoisomer \((7)\).

With these considerations in mind, we conceived of a modified route to \(9\) which would circumvent these issues of selectivity and which would pass through a key meso intermediate that we hoped would be a candidate for enantioselective desymmetrization. As will be seen, our modified synthesis of the iodolactone \((9)\) would diverge substantially from the previously reported synthesis of the compound. Accordingly, we first sought to establish the feasibility of the proposed new route in the racemic series. With an optimized route in place, we would then turn to issues of enantiomeric control.

In broad terms, our modified synthetic strategy would pass through the key meso intermediate \((13)\) (Scheme 2). Olefin epoxidation followed by intramolecular ring opening with one of the enantiotopically related primary alcohols would afford a chiral compound of the type \(14\). We favored this proposed transformation, in that it allows for the two primary alcohols \((c\) and \(d)\) and the two olefinic carbons \((a\) and \(b)\) of the meso compound \((13)\) to be concurrently differentiated in a regiocontrolled fashion. Thus, in \(14\), the olefinic carbon that has been converted to a secondary alcohol \((b)\) is located proximally to the primary alcohol that remains as such \((d)\). In addition to the regiochemical discrimination expected from the transformation, we hoped that this protocol would lend itself well to enantioselective desymmetrization. In any event, with the functionalities thus differentiated, intermediate \((14)\) should be readily advanced to \(15\). We anticipated that exposure of \(15\) to
Baeyer-Villiger oxidation conditions would result in regioselective migration of the tetrahydrofuranyl moiety α- to the ketone, as shown. Since both of carbon atoms which are α- to the keto function of intermediate (15) are trisubstituted, we could not be certain of obtaining sufficient levels of regioselectivity in the oxidative ring cleavage. Nonetheless, we postulated that the electron donating effect of the tetrahydrofuranyl moiety would render this group significantly better able to stabilize the cationic charge during the peroxide bond cleavage step. This mechanistic bias would result in selective formation of the desired compound (16) in which the ketone has been oxidized to a carboxylic acid, while the ether has been converted to a mixed acetal. We anticipated that 16 could then be converted to intermediate (17) through a series of standard transformations. Reflection on the outcome of the overall transformation of 13 to 17 illuminates the power of this degradative sequence. Thus, one of the olefinic carbons of 13 has been transformed to a secondary alcohol (b), while the other has been converted to an exocyclic methylene group (a). The diol of 13 has been similarly differentiated to a lactone functionality, such that one carbon has been oxidized to the lactone carbonyl (d), while the other remains in the alcohol oxidation state (c). Moreover, this transformation has been accomplished in a completely regiocontrolled fashion, so that the lactone carbonyl (d) is proximally located to the secondary alcohol (b) in 17. With issues of regio- and stereochemistry thus addressed, we expected that iodolactonization of 16 would afford the target compound (9).

Scheme 2. Proposed strategy for redesigned synthesis of iodolactone (9).

Thus, our first task would be the preparation of meso compound (13). As shown in Scheme 3, the synthesis commenced with the Diels-Alder reaction of substituted cyclopentadiene (18) and monomethyl maleic anhydride (19)\textsuperscript{14} to afford, upon methanolysis and esterification, the endo cycloadduct (20). We note that, although 2,3-dimethylmaleic anhydride (3) had served as an effective dienophilic coupling partner with diene (2) in the original route, our attempts to realize cycloaddition of 3 with the more hindered diene (18) were unsuccessful. In order to obtain the functional equivalent of the product of the cycloaddition with dimethylmaleic anhydride, we would need to develop a means to selectively deliver the second methyl group to the exo face of the molecule (20, see asterisk).

A solution to this problem presented itself in a paper by S. Ghosh and coworkers.\textsuperscript{15} The authors found that dimethylation of the unmethylated congener of 20 produced only two products – one in which both
methyl groups were exo and one in which both were endo. Importantly, the dialkylation proceeded to form exclusively syn dimethylated product. In our case, with one methyl group already installed in an exo orientation, we could be optimistic that C-alkylation would selectively give rise to 21, in which the newly installed methyl group would also be installed exo, with a syn relationship to the existing methyl group. In the event, we were pleased to find that diastereoselective lithium enolate mediated C-methylation of 20 proceeded with the expected diastereoselectivity to afford 21. This preference for delivery to the exo face may be attributed, in part, to steric effects, as the electrophile would favor approach of the enolate from the face opposite the pseudo axial ester functionality. Furthermore, it also seems not unlikely that the electron-withdrawing effect of the vicinal ester may induce electronic dissymmetry between the two faces of the enolate π-system at the alkylation site, rendering the endo face somewhat less nucleophilic. In any event, intermediate (21), the product of exclusive exo methylation, was converted to the key meso compound (13) in a straightforward manner, as shown.

Scheme 3. Preparation of key intermediate (13). a) 180 °C, neat; then MeOH, reflux, PhH/MeOH, TMSCHN₂, 92 % for one-pot reaction; b) LDA, HMPA, MeI, THF, -78 °C→rt, 95 %; c) LAH, THF, reflux; d) Na, NH₃, THF/EtOH, 72 % over two steps; e) 2,2-dimethoxypropane, acetone, p-TsOH; f) NaH, (EtO)₂POCH₂CO₂Et, THF, 86 % over two steps; g) Mg, MeOH, acidic workup, 77 %.

As we had anticipated, treatment of intermediate (13) with mCPBA led to the formation of 14, presumably through an epoxide intermediate. The latter was oxidized to 15, which, upon exposure to Baeyer-Villiger conditions, was converted exclusively to intermediate (16). We were pleased to find that the oxidation reaction proceeded with complete regioselectivity to afford only the desired product. According to plan, the resulting carboxylic acid was converted to a secondary alcohol with retention of stereochemistry through a carboxy inversion sequence, affording intermediate (24). Trapping of the masked aldehyde of 24 served to liberate the primary alcohol, which subsequently underwent lactonization to form compound (25). The latter was then advanced to intermediate (26), which underwent selective selenation at the primary alcohol to afford, after oxidative elimination, the requisite exocyclic olefin of compound (27). Finally, iodolactonization afforded the target compound (9). This sequence of reactions served to efficiently differentiate the functionalities of the meso compound (13) with complete regiocontrol. Thus, the regiochemical issues that we had encountered in the first-generation synthesis had been reconciled through this novel synthetic approach.
Having established an improved synthesis of the late stage intermediate (9) we returned to our primary objective of developing an enantioselective route to merrilactone A. As noted previously, it was our hope that the transformation of 13 to 14 would be amenable to enantioselective catalysis. Thus, intermediate (13) was treated with DMDO to afford the meso epoxide intermediate (28). At this point, we turned to the asymmetric ring opening methodology developed by Jacobsen and co-workers. Thus, 28 was treated with catalytic amounts of (R,R)-[CoIII(salen)]-OAc to afford intermediate (14) in 86% yield over the two steps. We were very pleased to find that this reaction proceeded with good levels of enantiocontrol, providing 14 in 86% ee. As expected, treatment of 28 with the opposite catalyst enantiomer provided ent-14 in the same yield and ee. The degradation route described, starting with 19, has been applied to each of the enantioenriched versions arising from enantioselective desymmetrization. At this writing, merrilactone A (1) and ent-merrilactone A (ent-1) have been reached in highly enantioenriched form.

Scheme 5. Desymmetrization of meso compound (13). a) DMDO, CH₂Cl₂, 0.5-1 h; b) (R,R)-[CoIII(salen)]-OAc, -78 °C, two days; then -25 °C, two days, THF, 86 % over two steps; c) (S,S)-[CoIII(salen)]-OAc, -78 °C, two days; then -25 °C, two days, THF, 85 % over two steps.
GUANACASTEPENE A
Isolated from an endophytic fungus found in the Guanacaste Conservation Area in Costa Rica, guanacastepene A (29) has generated a great deal of attention throughout the synthetic community. Initial excitement over reports of antibiotic-resistant bacterial activity has been tempered by subsequent findings that the observed hemolytic activity is the result of nonspecific membrane lysis. Nonetheless, the unique and intriguing structural elements of the guanacastepene framework have inspired a number of research groups, including our own, to launch programs directed to the synthesis of guanacastepene A.

Our own investigations, which culminated in the first reported total synthesis of (±)-guanacastepene A, have been described in detail elsewhere. An overview of the synthetic route to guanacastepene A is provided in Scheme 6. Thus, conjugate addition of isopropyl cuprate to 2-methylcyclopentenone (30) followed by alkylation produced intermediate (32) as a single diastereomer, as shown. Reductive cyclization of 32 provided intermediate (33), which, upon exposure to PCC, underwent oxidative rearrangement to afford cycloheptenone (34). Our plans to directly dialkylate intermediate (34) were frustrated by difficulties associated with the regeneration of the enolate following the first alkylation. Our solution to this problem made use of intermediate (35), obtained from 34 via an Eschenmoser salt Mannich protocol. Conjugate vinyl cuprate addition to the exocyclic olefin of 35 with concomitant trapping of the enolate provided silyl enol ether (36), which was then methylated to afford 37 as a single diastereomer. The latter was advanced to β-keto ester (38) through a series of straightforward transformations. Interestingly, although attempts to cyclize the non-epoxidized congeners of 38 were largely unsuccessful, intermediate (38) itself smoothly underwent facile tandem epoxide-opening, β-elimination and Knoevenagel cyclization to provide the tricyclic intermediate (39). Concomitant reduction of the ketone and ester functionalities, followed by Mitsunobu inversion of the resultant secondary alcohol afforded, upon protection of the newly formed diol, compound (40). The cyclopentenyl alcohol was deprotected and converted to a ketone, which, upon exposure to Rubottom conditions, underwent diastereoselective α-hydroxylation to afford intermediate (41). The latter was then readily converted to racemic guanacastepene A (29).

Having synthesized racemic guanacastepene A, we now focused on the task of developing an enantioselective route, by which we would be able to gain access to either antipode of the natural product. We also hoped to take this opportunity to address a weakness that had presented itself in the first-generation synthesis. Thus, in the reductive cyclization of 32, which led to the installation of the cycloheptenone ring system, we consistently observed significant levels of a noncyclized side product, wherein the iodide had been reduced to afford the proteo congener of 32. Under optimized reaction conditions, we were able to achieve ratios of cyclization product (33) to iodo-reduced side product of up
to 3.5:1. We were hopeful that we might be able to develop an improved protocol for the installation of the B-ring cycloheptenone system.

Scheme 6. Synthetic route to (±)-Guanacastepene A.

Given these considerations, we set as the target compound for our modified, asymmetric route, the cycloheptenone intermediate (34). With enantiomerically enriched 34 in hand, we were confident that the synthesis of optically active guanacastepene A could be achieved in a straightforward manner, according to the previously described first-generation route.

In the context of our initial studies toward guanacastepene A, we had considered variations of the homo-Robinson annulation in our attempts to prepare the fused cycloheptenone (34). These earlier efforts were unsuccessful, due to the desire of the annulation substrates to form cyclopentenone ring systems in preference to the requisite cycloheptenones. However, in redesigning our synthesis of 34, we once again came to favor a Robinson annulation approach to the formation of the bicyclic system. Our overall synthetic strategy would first entail a well-precedented Robinson annulation of a substrate of the type 42, itself obtained from methylcyclopentenone (30) via conjugate addition followed by enolate alkylation (Scheme 7). We envisioned the conversion of the cyclohexenyl Robinson
annulation adduct (43) to the target compound (34) through a series of transformations which would ultimately result in a one-carbon expansion of the cyclohexenone ring. We note that, although our initial synthetic investigations would be conducted in the racemic series, this modified route was designed with the expectation that asymmetry could eventually be achieved in the initial conjugate addition to compound (30).

![Scheme 7. Modified route to intermediate (34).](image)

In considering the ring expansion of 43, we took note of a four-step protocol developed by Saegusa and coworkers, involving the overall conversion of a cyclic ketone to its one-carbon expanded α,β-unsaturated congener, through FeCl₃-mediated oxidative cleavage of an intermediate silyloxydicyclopropane.³¹ We first sought to evaluate the feasibility of the Saegusa ring expansion strategy in the context of more complex fused cyclohexenone substrates of the type (43). Thus, our plan would require a compound of the type (44) to be converted to a cross-conjugated silyloxydiene (45), which would then undergo Simmons-Smith cyclopropanation to afford the corresponding silyloxydicyclopropane (46). It was our hope that, upon exposure to FeCl₃, oxidative cleavage would occur at the fused cyclopropyl bond to afford the ring expanded chloro ketone (47). Finally β-chloride elimination should provide the cross-conjugated dienone (48), which we anticipated would be amenable to selective olefin reduction of the disubstituted double bond.

![Scheme 8. Proposed route to homo-Robinson annulation adducts.](image)

Based on the precedent of Saegusa, we were optimistic that the critical oxidative cleavage reaction (cf. 46 → 47) would proceed with the desired regioselectivity at the bridging (tetrasubstituted) cyclopropyl bond to provide ring-expanded product, rather than at the trisubstituted bond, which would afford α-substituted cyclohexyl adducts. The observed ring-opening regioselectivity described by Saegusa et al. has been attributed to the action of a radical pathway. It is known that FeCl₃ mediated oxidative
cleavage of cyclopropanols proceeds via a radical mechanism, in which an alkoxy radical undergoes homolytic scission to afford a $\beta$-carbon radical species, which subsequently abstracts chlorine to afford the observed $\beta$-chloro ring opened product. In the absence of the experiment, it would be difficult to predict whether the $\alpha,\beta$-unsaturation of the ketone substrate would impact the directionality of the cyclopropyl ring opening reaction.

In the event, the viability of this ring expansion concept in the required sense was established with a series of fused cyclohexenone substrates. Importantly, the four-step protocol was implemented without purification of intermediates, to afford cross-conjugated dienones of the type (48) in approximately 40-45% overall yield from cyclohexenone substrates of the type (44).

Having thus developed an efficient means to effect a one-carbon ring expansion of a fused cyclohexenone, we now sought to apply this capability to the preparation of our target compound, intermediate (34). Our synthesis commenced with the Michael addition of racemic silyl enol ether (31) to methyl vinyl ketone to afford intermediate (42). The latter was converted to the fused cyclohexenone (43) under standard aldol cyclization conditions. Formation of the cross-conjugated silyloxydiene followed by cyclopropanation provided intermediate (50). Upon treatment with $\text{FeCl}_3$, the substrate underwent regioselective oxidative ring opening to afford, upon dehydrohalogenation, the cycloheptadienone (52). Finally, selective reduction of the disubstituted olefin was accomplished with Wilkinson’s catalyst to give rise to the target compound (34).

Scheme 9. Modified synthesis of intermediate (34). (a) MVK, AcOH, BF$_3$-Et$_2$O, -20°C, 97%; (b) NaOMe, 98%; (c) (i-Pr)$_2$NH, n-BuLi, TMSCl, THF, -78°C; (d) Et$_2$Zn, CH$_2$I$_2$, Et$_2$O, 0°C; (e) $\text{FeCl}_3$, 0°C; (f) NaOAc, reflux, 40% yield over 4 steps; (g) Wilkinson’s catalyst, H$_2$, 83%.

Having developed an alternate route to guanacastepene A intermediate (34), we now focused our attentions on the primary goal of realizing an asymmetric synthesis of 34. In this context, we hoped to make use of a disclosure by Quinkert et al. of a highly enantioselective conjugate addition of isopropenyl cuprate to methylcyclopentenone (30). Thus, under the Quinkert reaction conditions, substrate (30) was converted to 53 in excellent yield with 90% ee (Scheme 10). Formation of the silyl
enol ether, followed by Michael addition to methyl vinyl ketone proceeded with excellent diastereoselectivity to afford 54, as shown. Hydrogenation of the isopropenyl group provided the cyclization precursor (42). This intermediate was advanced to the optically active target compound (34) according to the sequence described above for the racemic series. Thus, the enantioselective formal synthesis of guanacastepene A has been accomplished.

Scheme 10. Enantioselective formal synthesis of guanacastepene A. (a) CuSCN, isopropenyllithium, (S)-2-methoxymethylpyrrolidine, 4Å MS, -100°C, 96%, 90% ee; (b) TBSOTf, TEA, 90%; (c) MVK, AcOH, BF₃·Et₂O, -20°C, 90%; (d) H₂, Pd/C, 92%; (e) NaOMe, 98%; (f) (i-Pr)₂NH, n-BuLi, TMSCl, THF, -78°C; (g) Et₂Zn, CH₂I₂, Et₂O, 0°C; (h) FeCl₃, 0°C; (i) NaOAc, reflux, 40% yield over 4 steps; (j) Wilkinson’s catalyst, H₂, 83%.

**CONCLUSIONS**

In summary, routes to optically active merrilactone A and guanacastepene A have been charted. Each synthetic program was initially focused on the total synthesis of a natural product in racemic form. With this objective accomplished, we then launched the second phase of the research program, in which we would begin to consider issues of enantiocontrol. It will be noted that, in both syntheses, the modified synthetic routes served the dual purpose of allowing access to enantiomerically enriched material and of providing a means to overcome weaknesses that had been identified in the first generation syntheses of the racemates. Thus, in the case of merrilactone A, our modified asymmetric route to the iodolactone intermediate (9) allowed us to circumvent two particularly problematic steps: the conversion of the anhydride to the lactone (4 → 5) and the Johnson orthoester Claisen rearrangement (6 → 7). Similarly, our newly developed asymmetric route to intermediate (34) in the guanacastepene A synthesis obviated the need for a troublesome reductive cyclization to form the fused cycloheptenone system (32 → 33).

In light of recent reports disclosing a membrane lysis mechanism of action for guanacastepene, we do not currently have plans to advance the optically activity intermediate (34) to enantioenriched
guanacastepene itself. We are, however, currently preparing both antipodes of merrilactone A according to our modified asymmetric route. The neurotrophic activity of each enantiomer will be evaluated, and the results will be reported in due course.

ACKNOWLEDGEMENTS
Support for this work is provided by the National Institutes of Health (Grant HL25848). H.Y. is grateful for a Predoctoral Fellowship from Eli Lilly & Company.

REFERENCES AND NOTES


20. Interestingly, the (R,R)-[CoIII(salen)]-OAc catalyst gave the opposite enantiomer than was expected based on comparison to the analogous Jacobsen case of an unsubstituted dihydroxymethyl cyclohexene oxide. Research is in progress to investigate this anomaly.


