SELECTIVE ATROPISOMER PREPARATION IN NATURAL PRODUCT SYNTHESIS

Reported by Kevin M. Peese September 16, 2002

INTRODUCTION

Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the barrier to rotation is high enough to allow for the isolation of the conformers.[1] Ōki has arbitrarily defined atropisomers to exist when the half-life of interconversion is greater than 1000 seconds, the time considered to be the minimum lifetime for a molecule to be isolable, although the term is used more flexibly in general usage.[2] Atropisomerism is significant because it introduces an element of chirality in the absence of stereogenic atoms. Consequently, atropisomers are of great importance in asymmetric synthesis, asymmetric catalysis, as well as natural product chemistry. Although there is great interest in the stereoselective synthesis of atropisomers, highly selective methods for their preparation remain sparse. This issue is particularly relevant in the realm of natural product chemistry, where total synthesis is hampered by the lack of general methods. This report will survey the existing strategies for atropisomer construction, taking examples from natural product synthesis.

CLASSES OF ATROPISOMERS

The first reported isolation of an atropisomer was in 1922 by Christie and Kenner.[3] Through a diastereoselective crystallization, 6,6'-dinitro-2,2'-diphenic acid (**1**) was resolved into its two entantiomers (Figure 1). Since then, atropisomerism has been observed in a large number of chemical entities.

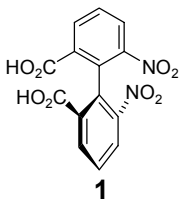

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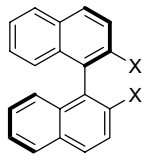
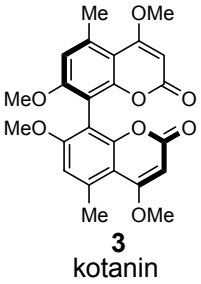
Figure 1. 6,6'-Dinitro-2,2'-diphenic acid.



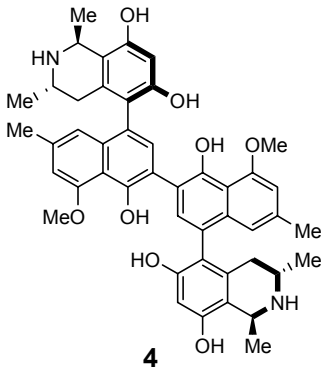
2

Figure 2. Example of binaphthyl ligands. (X=NH_2, OH, PPh_2)

Atropisomers are often broken down into several classes, based on the hybridization of the atoms of the hindered bond. The first and most common class of atropisomers is the sp^2-sp^2 family. This group is exemplified by biaryls that are either tri- or tetra- ortho substituted. Perhaps the best known members of this class of atropisomers are the binaphthyl ligands (**2**), which are commonly known as BINAPS and are widely used in asymmetric synthesis and catalysis (Figure 2). Within the realm of natural products, the biaryl motif is by far the most common form of atropisomerism. Two examples of natural products of this class are kotanin (**3**) and michellamine B (**4**) (Figure 3).[5-7]



3
kotanin



4
michellamine B

Figure 3. Kotanin and michellamine B.

Kotanin is particularly noteworthy, being a chiral molecule with no chiral atoms.

The sp^2-sp^3 class is rarely found in natural products, whereas the sp^3-sp^3 class usually occurs only in non-natural systems specially designed to hinder rotation.[1,2] Two examples of sp^2-sp^3 natural products are cordypyridone A (**5**) and its atropisomer cordypyridone B (**6**) (Figure 4).[8] The two molecules are formally diastereomers and, interestingly, only interconvert upon extended heating; they are conformationally stable at room temperature.

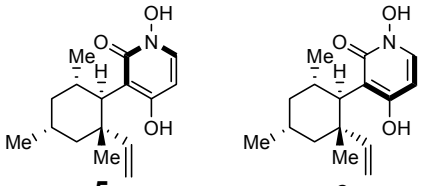


Figure 4. Cordypyridones A and B.

The last class of atropisomers is that created not by hindered rotation about a particular bond but rather by hindered rotation through the center of a macrocycle or by the conformational stability of a macrocycle. Examples from this class are longithorone B (**7**) and benzomalvins A (**8**) and D (**9**) (Figure 5).[9,10] In longithorone B, the quinone ring of the macrocycle does not rotate through the ring, so the system is conformationally stable. Attempted thermal equilibration of the atropisomers at 80 °C effected no change, whereas heating at 110 °C led only to decomposition. The benzodiazepine natural product, benzomalvin A, also exhibits atropisomerism; however, it is not configurationally stable. When isolated via reverse-phase HPLC, benzomalvin A equilibrated overnight to a 4:1 mixture with benzomalvin D.

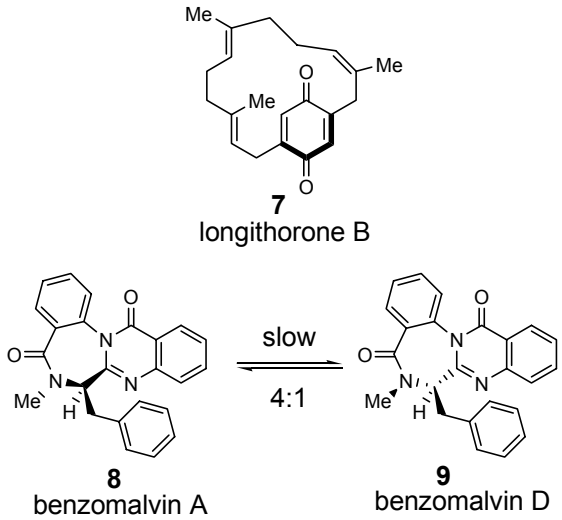


Figure 5. Longithrone B and benzomalvin A/D

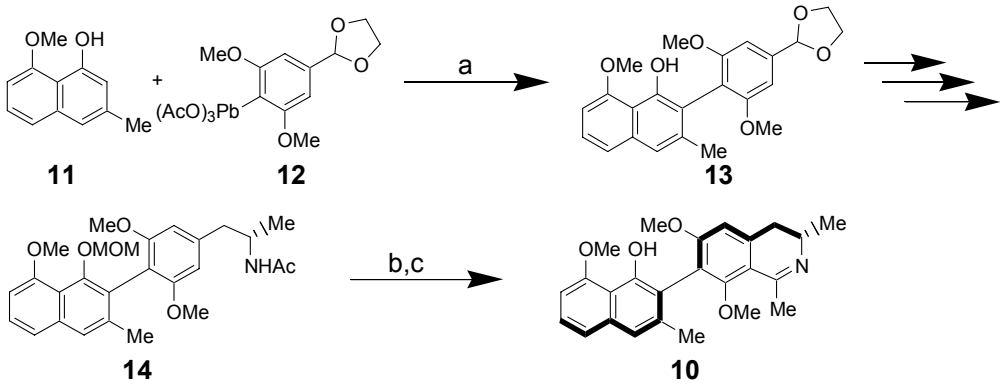
SYNTHETIC METHODS

Approaches Based on Resolution

Racemic synthesis followed by resolution is the method often employed for the synthesis of atropisomerically pure compounds. Although resolution is usually considered the least desirable option in asymmetric synthesis, because there is no control in the setting of stereocenters, resolution is often successful when other methods are not. One recent example is Morris' synthesis of anicistrocladidine.[11] Anicistrocladidine (**10**) presents an especially difficult challenge due to the axial chirality deriving from *meta* substitution on the dihydroisoquinoline ring of **10**. The key steps in the synthesis are oxidative coupling of naphthol **11** and aryl lead species **12** to form biaryl **13**, and subsequent electrophilic cyclization of biaryl **14** to form **10** (Scheme 1). The synthesis produces the symmetrical biaryl intermediate **13**. Only later, when phenethyl amine **14** is cyclized to form the dihydroisoquinoline **10**,

does the biaryl axis becomes chiral. The cyclization reaction functionally desymmetrizes the biaryl axis of **14**, albeit to a 1:1 ratio of diastereomers. Facile crystallization of the mixture of atropisomers provides **10** in enantiopure form. This synthesis is noteworthy in that current synthetic technology offers no simple methods to synthesize **10** selectively.

Scheme 1[a]



[a]Reagents: (a) Pyridine, CH_2Cl_2, 63%; (b) $POCl_3$, 2-4-6-collidine, CH_3CN, reflux, 74%;
(c) diastereoselective recrystalization from toluene/ petroleum ether (atropisomer resolution)

Approaches Based on Thermodynamic Equilibration

One distinct difference between atropisomeric chiral centers versus chiral carbons is that the former can be equilibrated *thermally,* whereas the latter must be equilibrated *chemically*, i.e. by making/breaking chemical bonds. This creates the advantageous circumstance in molecules possessing both types of chiral centers of being able to selectively equilibrate either the atropisomeric chiral center(s) or the chiral carbon(s) to give the thermodynamically more stable diastereomer. This strategy has been used with great success in several cases.[12] The most prominent of these is the total synthesis of the vancomycin aglycon (*vide infra*).

Vancomycin (**15**) is an exceedingly complex glycopeptide antibiotic (Figure 6). The aglycon of **15** possesses three centers of atropisomeric chirality: the axial chirality of phenyl rings 1 and 2, the planar chirality of phenyl ring 3, and the planar chirality of phenyl ring 5. Together, these atropisomeric moieties add exceptional challenge to an already formidable synthetic problem. Three groups have successfully completed the synthesis of the aglycon: those of Boger, Evans, and Nicolaou. [13,14,15] The Evans and Boger groups used thermodynamic equilibration as their guiding strategy to control atropisomer formation with moderate to good success, while the Nicolaou group relied on simple separation of atropisomers.

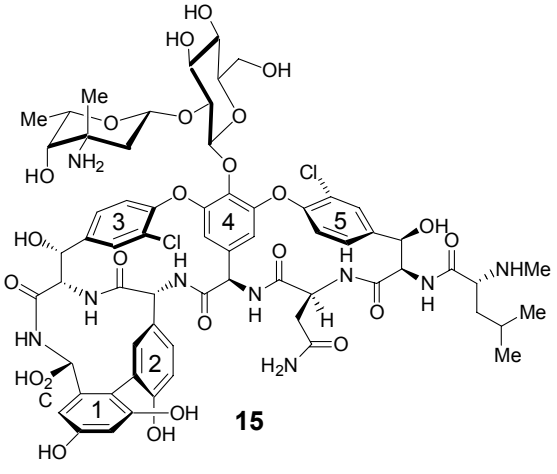
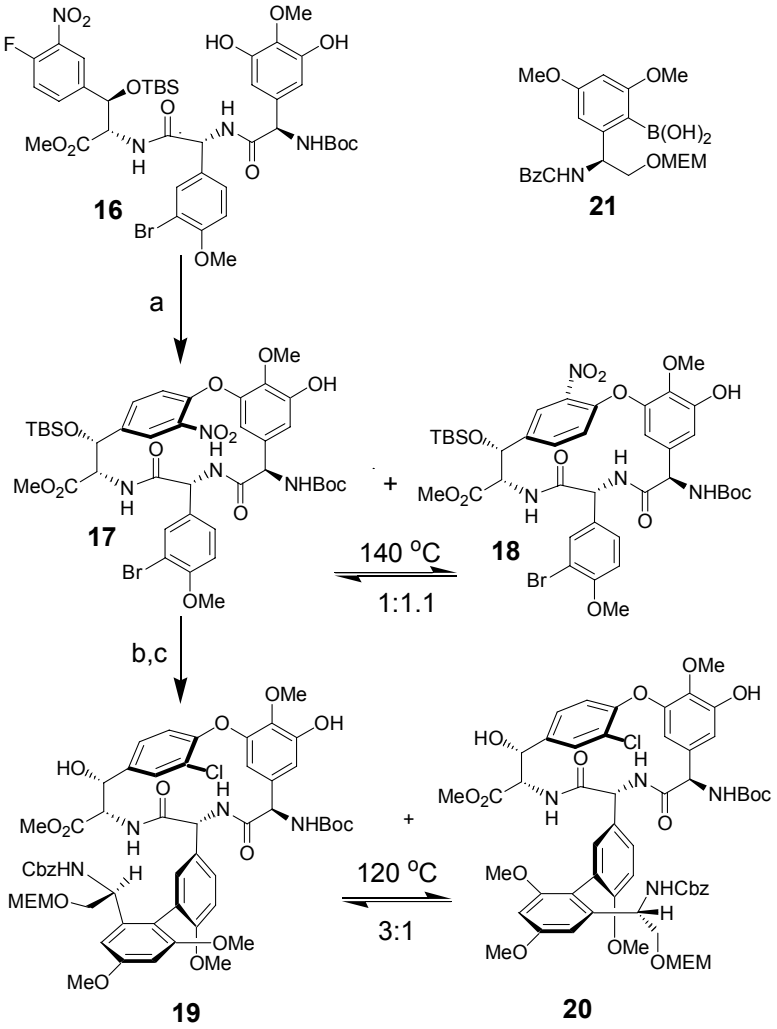


Figure 6. Vancomycin.

In Boger's synthesis of the aglycon of **15**, extensive investigations into the thermodynamically preferred orientations of numerous intermediates as well as the energies of activation of these equilibrations guided the choice of reaction order as well as intermediates.[13] Thus, acyclic peptide **16** was cyclized to a 1:1 ratio of atropisomers **17** and **18** (Scheme 2). While this reaction shows no atropselectivity, the undesired product is easily separated and equilibrated to a 1:1.1 mixture of **17** and **18**. This allows for efficient recycling of the undesired atropisomer. In a similar fashion, reduction and chlorination of **17** followed by Suzuki coupling with boronic acid **21** gives biaryls **19** and **20** in a 1:1.3 ratio. This ratio may be improved to a 3:1 ratio via thermal equilibration without equilibrating the chlorophenyl ring. Similar to undesired atropisomer **18**, undesired atropisomer **20** may be recycled to desired isomer **19**.

Scheme 2[a]



[a]Reagents: (a) $K_2CO_3/CaCO_3$, 63%, 1:1 atropisomers; (b) Reduction then Sandmeyer reaction; (c) **21**, $Pd_2(dba)_3$, (*o*-tolyl)$_3$P, 88%, 1:1.3 atropisomers.

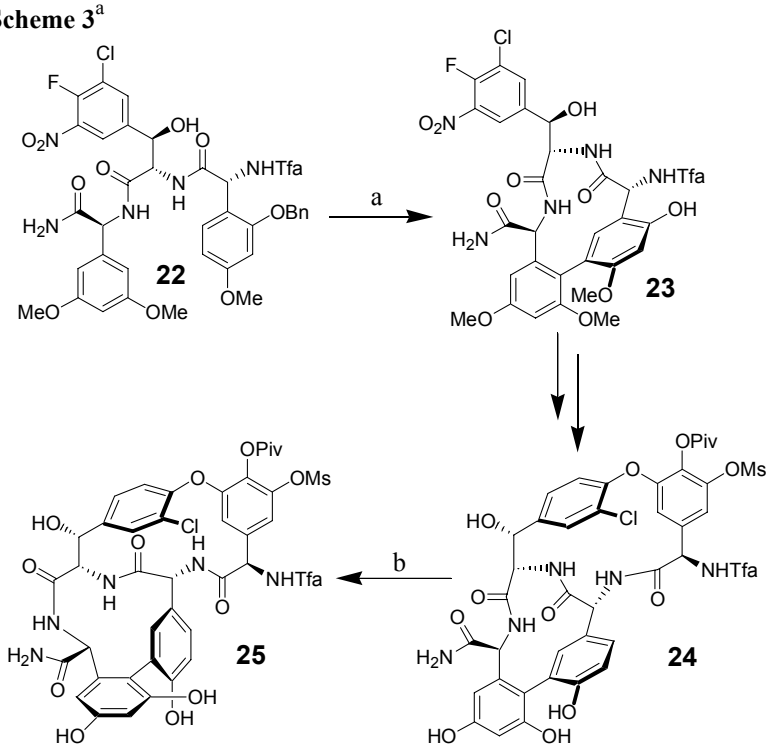
While Boger focused primarily on thermal equilibration of the individual atropisomeric centers, Evans recognized that global structure might significantly affect the thermodynamic preferences of the individual atropisomers.[14] Following this strategy, acyclic peptide **22** was cyclized to macrocycle **23** in >95:5 selectivity for the *unnatural* atropisomer (Scheme 3). The control element of the cyclization was found to be A(1,3) strain between the benzylic NTfa group and the ortho O-benzyl functionality. Extensive preliminary investigations showed that the second macrocycle could be constructed from the unnatural atropisomer **23** to give **24** with good selectivity. With the second macrocycle in place, bis-macrocycle **24** showed a strong thermodynamic preference for the *natural* biaryl atropisomer and hence, could easily be equilibrated to **25**. Although thermodynamic strategies can certainly be highly

successful, they usually require very involved model studies. As a result, direct synthesis of atropisomers exercising active control of selectivity is much more desirable.

Substrate Control: Acyclic Auxiliaries

The first reliable auxiliaries for atropisomeric coupling of binaphthyls were chiral oxazolines. Meyers pioneered this methodology during his extensive investigations of oxazolines as general chiral directing groups.[16] Aryl oxazolines have been used both in nucleophilic aromatic substitution reactions with Grignard reagents and in Ullman coupling reactions. In the case of the Ullman reaction, however, the selectivities appear to be derived from thermal equilibration of the kinetic products.[17] An example of the use of oxazolines in atropisomeric natural product synthesis can be found in Rizzacasa's synthesis of (-)-O-methylancistrocladine (**26**).[18] The key step of the synthesis is the nucleophilic aromatic substitution reaction between Grignard reagent **27** and oxazoline **28** to give biaryl **29** with 92:8 atropselectivity (Scheme 4). The rationale for the selectivity can be seen in proposed transition state **30**, in which the oxazoline isopropyl group blocks approach from the lower face of naphthyl oxazoline **30** (Figure 7).

Scheme 3[a]



[a]Reagents: (a) VOF_3, $BF_3{\cdot}Et_2O$, $AgBF_4$,TFA/ CH_2Cl_2, 0 ^oC, then $NaHB(OAc)_3$, 65%, <95:5 atropisomers; (b)MeOH, 55 ^oC, <95:5 atropisomers.

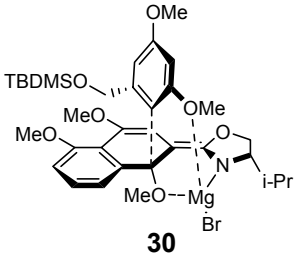
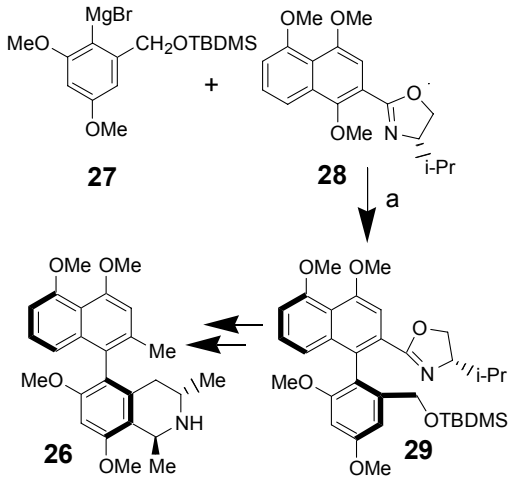


Figure 7. Transition state **30**.

More recently, chiral chromium complexes have been used as chiral auxiliaries. These complexes often give exquisite atropselectivity, and the biaryl products are easily liberated from the chromium tri-carbonyl moiety. An example of the use of this

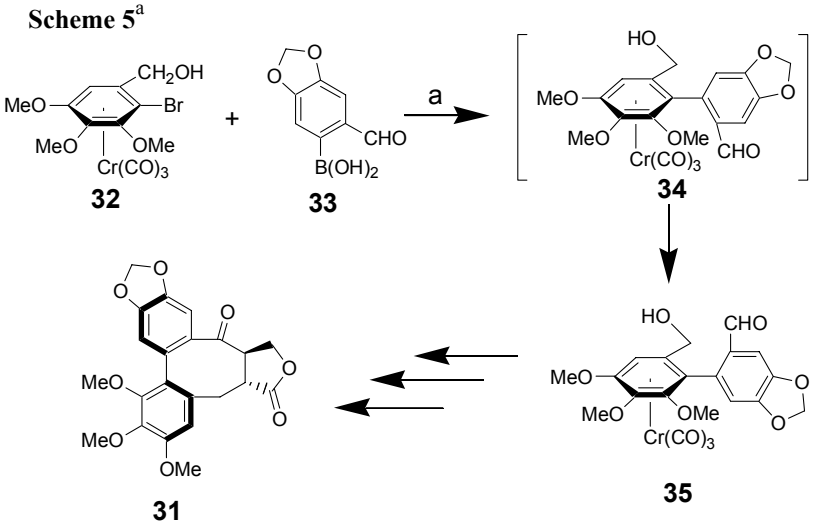
Scheme 4[a]



[a]Reagents: (a) THF, Δ, 76%, 92:8 atropisomers.

strategy is the synthesis of (-)-steganone (**31**) by Uemura (Scheme 5).[19] Suzuki coupling of chromium aryl bromide **32** with boronic acid **33** affords biaryl **34** as the initial kinetic product, which then equilibrates to the thermodynamic product **35**. A serious limitation to this methodology is the difficult preparation of enantiopure chromium arene complexes.

Scheme 5[a]



[a]Reagents: (a) $Pd(PPh_3)_4$, Na_2CO_3, MeOH, H_2O, reflux, 1 hr, 67%, single atropisomer.

In another approach, benzylic A(1,3) strain has been used to control atropisomerism of aromatic rings.[20] In this approach, steric repulsion between a benzylic substituent and an ortho group strongly influences the orientation of the aromatic ring (Figure 8). This approach was used with success in Shair's synthesis of longithorone A (**36**) (Scheme 6). Acyclic alkyne **37** was cyclized with Grubbs catalyst to give the enyne metathesis product, macrocycle **38**. The benzylic OTBS group serves as a removable auxiliary to control atropselectivity of the ring closure through an unfavorable A(1,3) interaction with the ortho OTBS group.

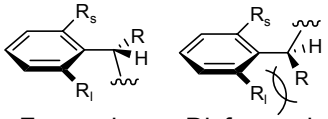
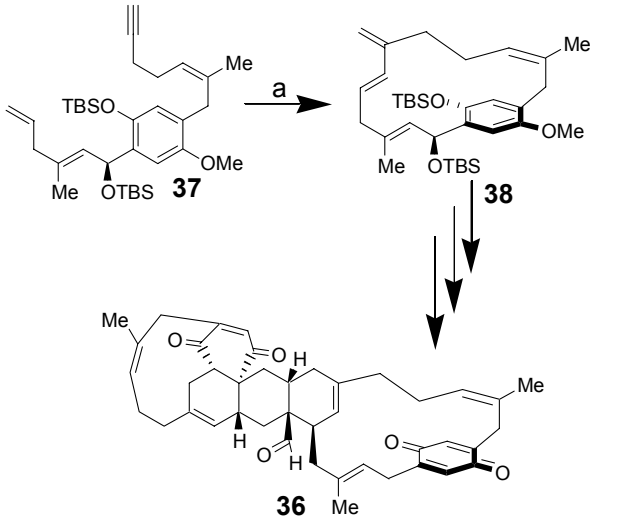


Figure 8. Benzylic A(1,3) strain.

Scheme 6[a]



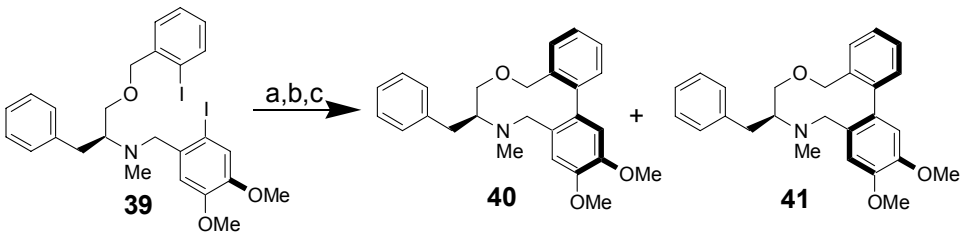
[a]Reagents: (a) 0.5 eq. $(Cy_3P)_2Cl_2RuCHPh$, ethylene (1 atm), CH_2Cl_2, high dilution, 42%, >20:1 atropisomers.

Substrate Control: Cyclic Auxiliaries

Cyclic auxiliaries have long been recognized as efficient tools for control of atropselectivity. Recently, Schreiber has elegantly demonstrated the power of cyclic substrates in his work towards diversity-oriented libraries.[22] The power of this methodology lies in the inherent high kinetic atropselectivity of many reactions. Often, these products are thermodynamically disfavored, allowing access to both atropisomers if the kinetic products can be equilibrated. For example, acyclic diiodide **39** can be oxidatively cyclized to a mixture of atropisomers; kinetic selectivity strongly favors **40**, whereas

thermodynamic selectivity favors **41** (Scheme 7). Many removable auxiliaries have also been used to the same effect: atropselectivity can often be controlled through macrocyclic conformations.

Scheme 7[a]

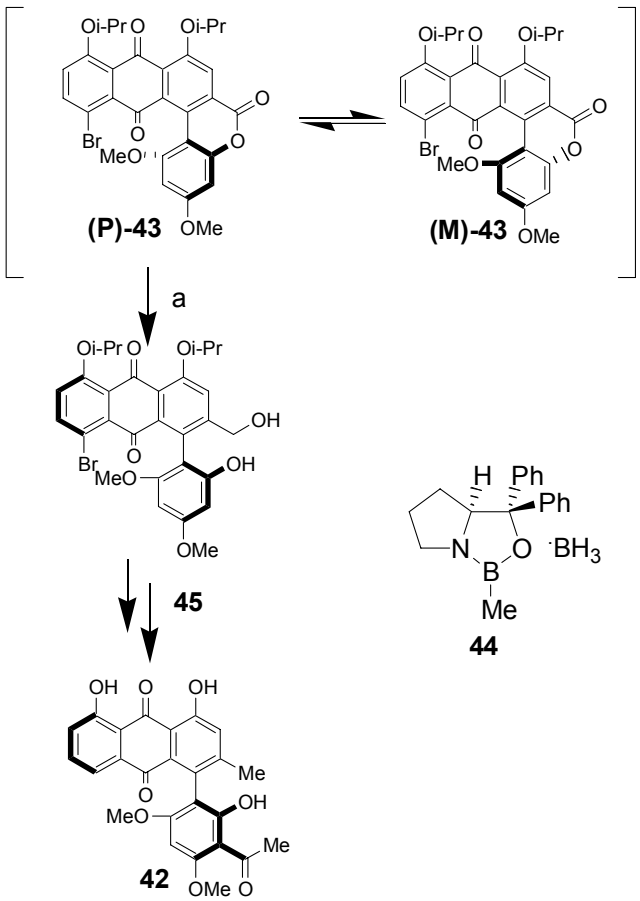


[a]Reagents: (a) t-BuLi, 2-MeTHF; (b) CuCN; (c) 1,3-DNB, 92%.
40:**41**: kinetic atropselectivity 16:1, thermodynamic atropselectivity 1:11.

Reagent Control

Only one reagent-based atropselective method has been used in natural product synthesis: the "lactone method" developed by Bringmann.[23] This method is based on the dynamic kinetic resolution of biaryl lactones by chiral reagents. In the synthesis of knipholone (**42**), conformationally unstable biaryl lactone **43**, is kinetically differentiated by and selectively reduced with Corey's oxazaborolidine-borane (**44**) to give benzyl alcohol **45** (Scheme 8).[24]

Scheme 8[a]



[a]Reagents: (a) **44**, BH_3, 0 ^oC, THF, 1 hr, 81%, 98:2 atropisomers.

CONCLUSION

The field of atropselective tranformations continues to develop rapidly. Recently, progress has been made in asymmetric Suzuki couplings to make biaryls ligands atropselectively.[25] Additionally, other asymmetric biaryl couplings have also appeared. Although these methods have yet to be applied to natural product synthesis, it is inevitable that they soon will be.

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