

A Continuum of Progress: Applications of N-Heterocyclic Carbene Catalysis in Total Synthesis

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Homogeneous catalysis · natural products ·
N-heterocyclic carbenes · synthetic methods ·
total synthesis

N-Heterocyclic carbene (NHC) catalyzed transformations have emerged as powerful tactics for the construction of complex molecules. Since Stetter's report in 1975 of the total synthesis of *cis*-jasmon and dihydrojasmon by using carbene catalysis, the use of NHCs in total synthesis has grown rapidly, particularly over the last decade. This renaissance is undoubtedly due to the recent developments in NHC-catalyzed reactions, including new benzoin, Stetter, homoenolate, and aroylation processes. These transformations employ typical as well as Umpolung types of bond disconnections and have served as the key step in several new total syntheses. This Minireview highlights these reports and captures the excitement and emerging synthetic utility of carbene catalysis in total synthesis.

1. Introduction

The inspiring structures and potential application of natural products have propelled scientists to pursue the total synthesis of bioactive molecules through the development of new synthetic methods. A current challenge for this high-value activity is the integration of new catalytic bond-forming tactics and strategies that enhance efficiency and provide rapid access to target compounds. In this regard, N-heterocyclic carbene (NHC) catalysis has emerged as a powerful method in organocatalysis to fashion new bonds with high levels of stereoselectivity through Umpolung as well as normal polarity based transformations. Until recently, total syntheses involving carbene catalysis were rare, presumably because of the restricted substrate scopes of established benzoin and Stetter NHC manifolds and the dearth of different reaction classes, which are now rapidly emerging. In this Minireview, the recent applications of NHC catalysis in the construction of natural products are summarized.

2. NHC-Catalyzed Benzoin Condensations

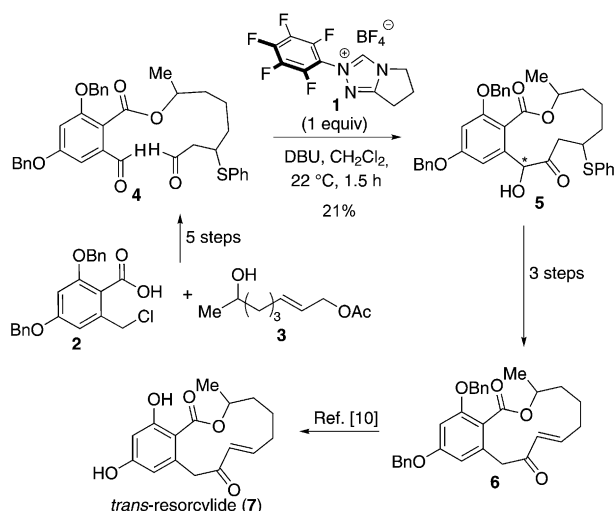
The coupling between two aldehydes or an aldehyde and ketone, also known as the benzoin condensation, is the most venerable of Umpolung reactions, which is used for the preparation of acyloins.^[1] In 1832, Wöhler and von Liebig reported the use of cyanide to promote the benzoin condensation.^[2] In 1943, Ugai et al. demonstrated that NHCs generated from the corresponding thiazolium precursor can serve as effective catalysts in this unusual reaction.^[3] Since this discovery, N-heterocyclic carbenes have been employed to catalyze numerous benzoin condensation reactions, including those of enolizable aldehydes and ketones, as well as the cross-benzoin reaction.^[4] To further enhance the synthetic utility of the benzoin reaction, the research groups of Sheehan,^[5] Enders,^[6] and others^[7] have developed asymmetric variants of this process by using chiral NHCs.

2.1. Synthesis of *trans*-Resorcyllide

trans-Resorcyllide (**7**) is a 12-membered macrocyclic lactone which belongs to a family of naturally occurring benzoic acid derived macrolide plant-growth inhibitors isolated from *Penicillium* sp. in 1978.^[8] In 2007, Mennen and Miller reported a formal synthesis of *trans*-resorcyllide through an NHC-mediated benzoin macrocyclization.^[9] Activation of the aliphatic aldehyde by the NHC generated from azolium salt **1** was preferred over the *ortho*-substituted benzaldehyde, and gave rise to macrolactones of type **5** as the only product. The synthesis began by a five-step reaction sequence to prepare thioether dialdehyde **4** from alcohol **3**

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and benzoic acid **2**. A subsequent intramolecular benzoin condensation afforded macrolactone **5** as a mixture of diastereomers in 21% yield (Scheme 1). The benzylic hydroxy group was subsequently removed through an acylation/deoxygenation sequence, and elimination of the sulfone led to dibenzylated *trans*-resorcylic **6**.^[10]

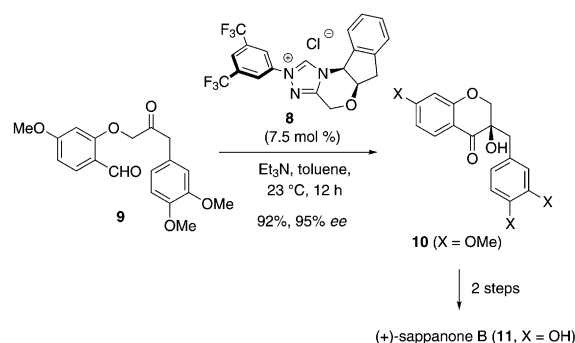


Scheme 1. Macrolactonization used by Mennen and Miller in the preparation of *trans*-resorcylic. Bn = benzyl, DBU = 1,8-Diazabicyclo-[5.4.0]undec-7-en..

2.2. Synthesis of (+)-Sappanone B

(+)-Sappanone B (**11**) is a homoisoflavanoid isolated from the heartwood of *Caesalpinia sappan* Leguminosae.^[11] This 3-hydroxychromanone has inhibitory activity towards

xanthine oxidase.^[12] In 2007, Takikawa and Suzuki reported the total synthesis of (+)-sappanone B.^[13] Ketoaldehyde **9** was obtained in five steps from commercially available 3-methoxysalicylic acid. Aldehyde **9** underwent a smooth intramolecular benzoin reaction in the presence of triazolium salt **8** and triethylamine within 12 h to produce methylated (+)-sappanone B (**10**) in 92% yield with 95% *ee* (Scheme 2).



Scheme 2. Synthesis of (+)-sappanone B.

The incorporation of the 3,5-trifluoromethyl substituents on the triazolium-derived NHC are notable and were tuned for optimal selectivity for the asymmetric transformation. Demethylation of **10** gave (+)-sappanone B (**11**) in 59% overall yield over eight steps.

2.3. Synthesis of Cassialoin

Cassialoin (**17**) is an anthrone C-glycoside isolated from the plant extracts of *Cassia garrettiana*.^[14] It is also found in



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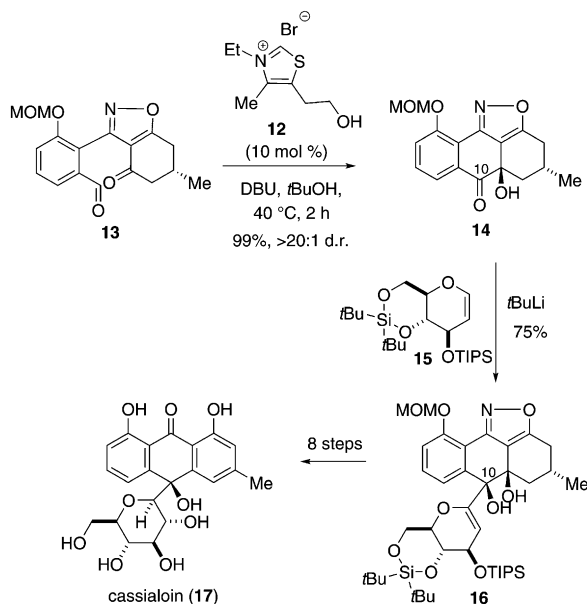


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the roots of *Rheum emodi*^[15] and the Chinese herb *Rumex dentatus*.^[16] The unique structural features of cassialoin include a phenolic anthraquinone skeleton stereogenically attached to a β -glycoside. Cassialoin has been identified in *in vivo* biological studies to inhibit tumor growth and metastasis in mice.^[17] In 2007, Suzuki and co-workers reported the first stereoselective total synthesis of cassialoin.^[18] The diastereoselective assembly of the anthraquinone skeleton was accomplished by an intramolecular NHC-catalyzed benzoin condensation. The treatment of ketoaldehyde **13** with 10 mol % of thiazolium salt **12** and DBU at 40 °C for 2 h gave ketol **14** in 99 % yield with excellent diastereoselectivity (Scheme 3). The lithium anion of glycal **15** was added to

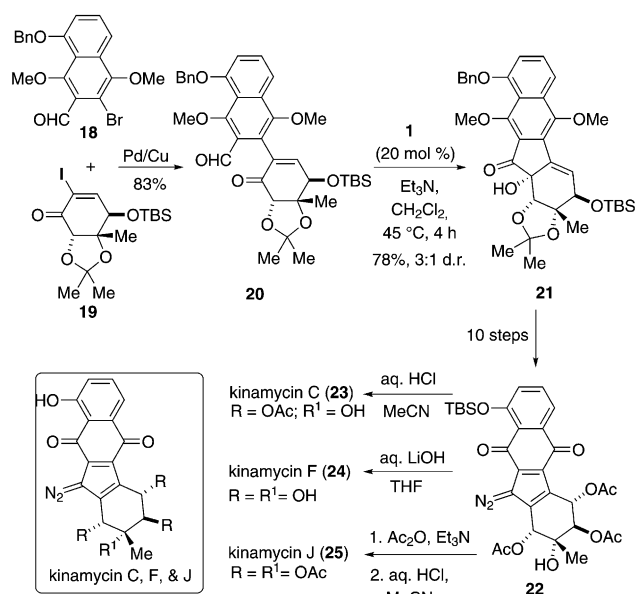


Scheme 3. Synthesis of cassialoin by Suzuki and co-workers. MOM = methoxymethyl, TIPS = triisopropylsilyl.

ketone **14** to afford *cis*-diol **16** as a single diastereomer. An additional eight steps gave the natural product cassialoin (**17**). The completion of this synthesis confirmed the originally proposed structure of cassialoin.^[14]

2.4. Synthesis of the Kinamycins and the Monomeric Unit of the Lomaiviticin Aglycon

The kinamycins^[19] and lomaiviticins A and B^[20] are natural products with antibiotic and antitumor activities. These natural compounds are structurally novel, with a diazofluorene group and a densely oxygenated cyclohexane ring. Lomaiviticins are dimers of a diazofluorene structure similar to the kinamycins. Kinamycins A–D were isolated from the fermentation broth of *Streptomyces murayamaensis*.^[19] In 2007, Nicolaou et al. reported a synthesis of kinamycins C, F, and J.^[21] An Ullmann coupling between bromide **18** and iodide **19** afforded aldehyde **20** on a multigram scale. Aldehyde **20** underwent a benzoin condensation in the presence of azolium **1** to yield cyclopentanone **21** in 78 %



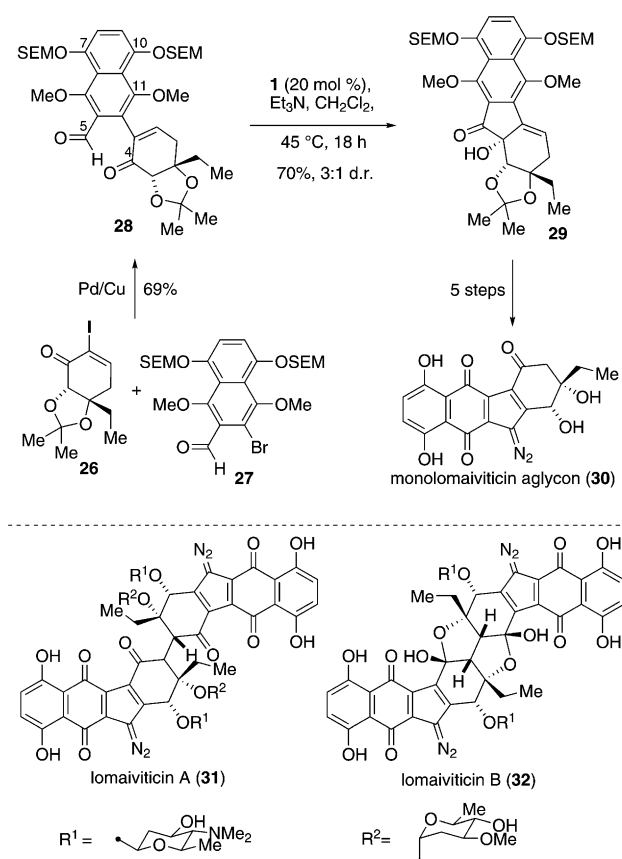
Scheme 4. Total synthesis of kinamycins C, F, and J by Nicolaou et al. TBS = *tert*-butyldimethylsilyl.

yield and with 3:1 d.r. (Scheme 4). A subsequent ten steps afforded diazofluorene **22**. A selective hydrolysis or selective manipulations of the acetate led to the three kinamycins (**23**–**25**) in yields between 9 and 11 % from the Ullmann coupling.

Lomaiviticins A (**31**) and B (**32**) are dimeric natural products isolated from *Micromonospora lomaivitiensis* that exhibit impressive antitumor and antibiotic activities against a variety of cancer cell lines and bacteria, respectively. In particular, lomaiviticin A has IC₅₀ values ranging from 0.01 to 98 μ M against numerous cancer cell lines.^[20] In 2009, Nicolaou et al. reported an enantioselective route to the monomeric unit of lomaiviticin aglycon (**30**).^[22] The structural similarities between the lomaiviticin aglycon and the kinamycins allowed them to apply a similar synthetic approach that was employed for the kinamycins (see above). Unfortunately, the attempted NHC-catalyzed benzoin condensation with bromide **18** (Scheme 4) resulted in the Stetter product as the major component. To circumvent this problem, the synthesis was re-engineered by using bromide **27**, which has SEM ethers at C7 and C10. These SEM groups would force the OMe group at C11 towards the C4 carbonyl group, thus rotating the bond between the two cyclic systems, and thereby allowing the acyl anion to favor the benzoin pathway. The treatment of ketoaldehyde **28** with NHC generated from azolium salt **1** afforded benzoin product **29** with excellent chemoselectivity (>20:1 d.r.; Scheme 5). Other more sterically demanding groups afforded lower selectivities or were not compatible with the necessary previous Ullmann coupling step. A subsequent five steps led to lomaiviticin aglycon in 16.5 % yield over nine steps.

2.5. Synthesis of Seragakinone A

Seragakinone A (**39**) was isolated from an unidentified marine fungus in symbiosis with rhodophyta *Ceradictyon*

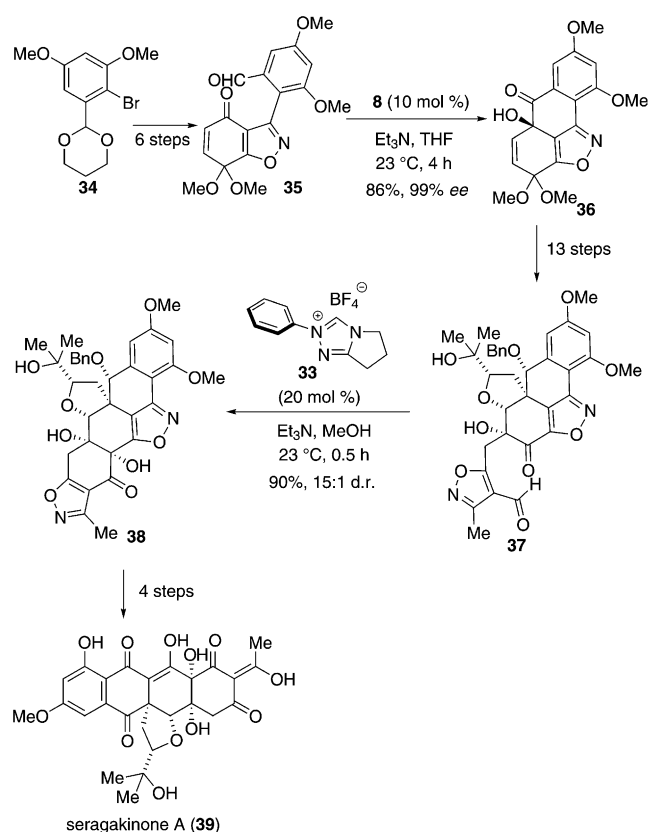


Scheme 5. Synthesis of the lomaivitins by Nicolaou et al. SEM = 2-(trimethylsilyl)ethoxymethyl.

spongiosum,^[23] and has shown antifungal and antibacterial activity. This natural product contains a densely oxygenated pentacyclic core with a prenyl group situated in a sterically hindered angular position. In 2011, Suzuki and co-workers reported an enantioselective synthesis of (–)-seragakinone A (**39**), with two of the key reactions used to fashion the tetracyclic core being benzoin condensations.^[24] The synthesis began with a six-step sequence to convert aryl bromide **34** into aldehyde **35**. The treatment of aldehyde **35** with triazolium salt **8**^[25] and triethylamine afforded tetracyclic compound **36** in high yield (86%) with excellent enantioselectivity (99% *ee*; Scheme 6). Thirteen subsequent steps afforded ketoaldehyde **37**. A second benzoin condensation using triazolium salt **33**^[26] furnished ketol **38** in 90% yield with excellent diastereoselectivity. The stereochemistry of ketol **38** was verified by X-ray crystallographic analysis. Four additional steps furnished seragakinone A (**39**) in a total of 26 steps and 2.3% overall yield.

3. The Stetter Reaction

The conjugate addition of acyl anion equivalents to α,β -unsaturated carbonyl compounds is commonly known as the Stetter reaction.^[27] This reaction offers a straightforward route for the synthesis of 1,4-dicarbonyl compounds, which are important intermediates in synthesis.^[28] Although there

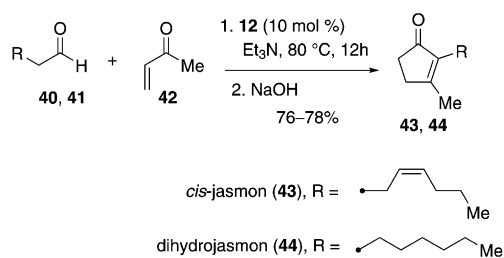


Scheme 6. Total synthesis of seragakinone A by Suzuki and co-workers.

have been significant advances in asymmetric intramolecular Stetter reactions by the research groups of Enders,^[29] Rovis,^[30] and Hamada,^[31] intermolecular Stetter reactions are inherently more challenging and further exploration is still needed. Typically, more activated substrates must be used, such as alkylidene malonates,^[32] nitroalkenes,^[33] or β,γ -ketoesters,^[34] to achieve selective intermolecular variants. In many of these intermolecular variants, self-condensation or benzoin by-products are common side reactions. Successful strategies to suppress these undesired reactions with triazolium-derived NHC catalysis include the use of α -keto carboxylates or acylsilanes^[35] as acyl anion precursors.^[36] This section includes reports of successful total and formal syntheses involving NHC catalysis in Stetter reactions.^[37]

3.1. Synthesis of *cis*-Jasmon and Dihydrojasmon

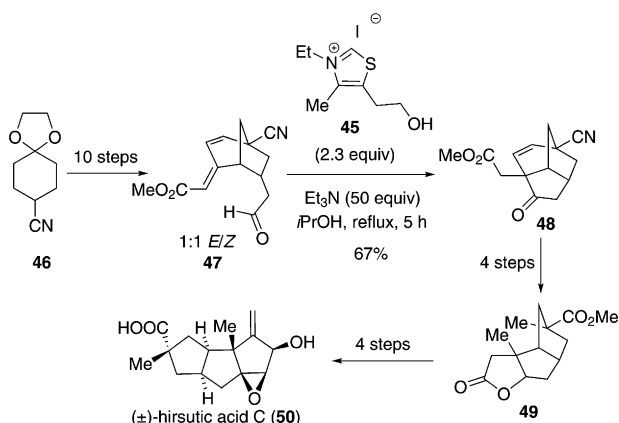
Naturally occurring *cis*-jasmon (**43**) and the related compound dihydrojasmon (**44**) are used as fragrance agents.^[38] In 1975, Stetter and Kuhlmann reported the total syntheses of these two natural products (Scheme 7).^[39] The routes involved a triazolium-catalyzed (**12**) intermolecular addition of saturated aldehydes **40** or **41** to methyl vinyl ketone **42** and aldol condensation to form *cis*-jasmon (**43**) and dihydrojasmon (**44**). To the best of our knowledge, this report describes the first application of the Stetter reaction in total synthesis.



Scheme 7. Synthesis of *cis*-jasmon and dihydrojasmon by Stetter and Kuhlmann.

3.2. Synthesis of (±)-Hirsutic Acid C

Hirsutic acid C (**50**) is a tricyclic sesquiterpene and is a highly congested complex natural product with seven stereogenic centers, six of which are contiguous. The members of this family possess both antibiotic and antitumor activity.^[40] In a seminal demonstration of the utility of the Stetter reaction to form polycyclic structures in syntheses, Trost et al. reported in 1979 the first stereocontrolled synthesis of (±)-hirsutic acid C (**50**).^[41] The synthesis began with a ten-step reaction sequence to convert cyanocyclohexane **46** into polycyclic aldehyde **47** (Scheme 8). Treatment of aldehyde

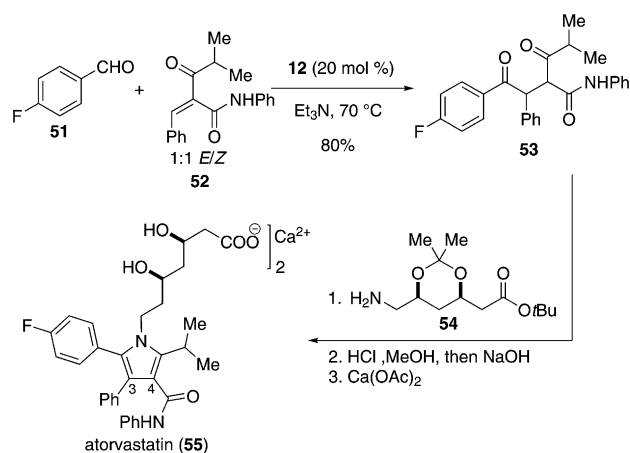


Scheme 8. Synthesis of (±)-hirsutic acid C.

47 with 2.3 equivalents of the thiazolium salt **45** and a large excess of triethylamine afforded the tricyclic ketone **48** in 67% yield. Reduction of the ketone in tricycle **48**, γ -lactonization, and an ozonolysis/reduction protocol furnished lactone **49**, thereby delivering the core of hirsutic acid. A subsequent four-step reaction sequence yielded hirsutic acid C in a total of 19 steps and 3.4% overall yield.

3.3. Synthesis of the Core of Atorvastatin

Atorvastatin calcium is a drug that has been marketed under the trade name Lipitor since 1997 by Pfizer. Lipitor is one of the most successful drugs in history and belongs to the statin drug class that is used to control cholesterol levels in the blood by inhibition of the HMG-CoA enzyme. It contains a tetrasubstituted pyrrole with an *N*-alkyl chain bearing a 1,3-



Scheme 9. Synthesis of Atorvastatin (Lipitor).

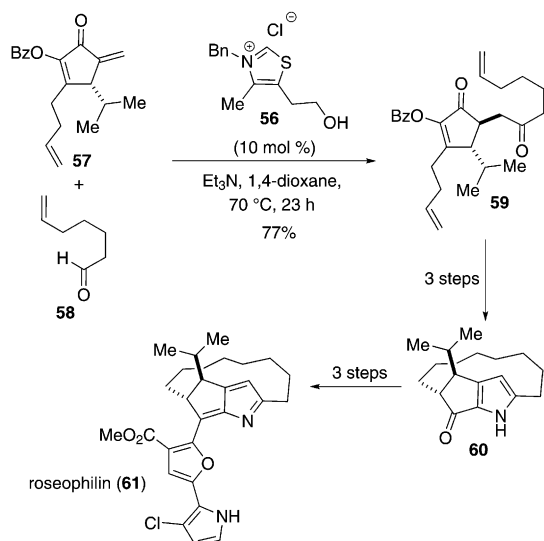
chiral diol and a terminal carboxylic acid (Scheme 9). QSAR studies led to the incorporation of phenyl and phenylamide moieties at positions 3 and 4 to increase the drug activity.^[42] The synthesis outlined by Roth et al. involves a Stetter reaction between *p*-fluorobenzaldehyde (**51**) and carboxamide **52** to furnish the desired 1,4-diketone **53** in 80% yield. A subsequent optimized Paal–Knorr reaction with heptanoate amine **54** afforded atorvastatin (**55**).^[43] This route is notable given the significant scale of this Umpolung reaction and since it involves fine tuning of the reaction partners to avoid any undesired benzoin reaction of the aldehyde (**51**).

3.4. Synthesis of Roseophilin

Roseophilin (**61**) was isolated from the fermentation broth of *Streptomyces griseo Viridis*.^[44] Roseophilin contains an azafulvene moiety conjugated to a pyrrolylfuran and an ansa macrocycle. The potent biological activity and unique structure have made it a popular target for synthesis.^[45] In 1999, Harrington and Tius reported a 12-step formal synthesis of roseophilin and obtained the racemic core of **60**.^[46] Two years later, the authors reported an enantioselective variant. The key step of the synthesis was the formation of cyclopentenone **57** by a Nazarov cyclization reaction. Treatment of unsaturated ketone **57** with two equivalents of 6-heptenal (**58**), thiazolium **56**, and triethylamine afforded the Stetter product **59** in good yield and in favor of the *trans* isomer (Scheme 10). Ring-closing metathesis, a selective olefin hydrogenation, and a subsequent Knorr reaction afforded the enantiopure roseophilin core **60**. An alkylation of the corresponding difuryl compound with the ansa core completed the synthesis of roseophilin (**61**) in 15 steps and 7% overall yield.^[47]

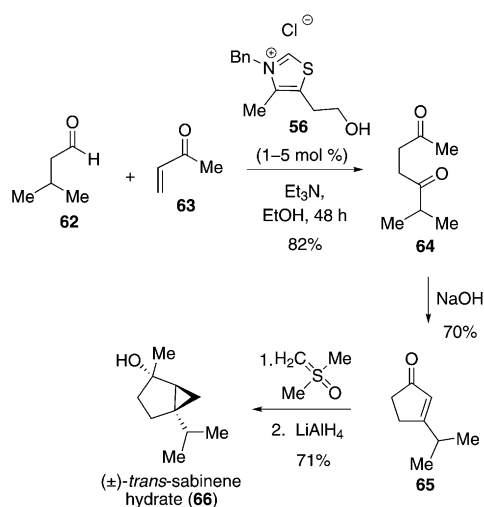
3.5. Synthesis of (±)-trans-Sabinene Hydrate

The natural product *trans*-sabinene hydrate (**66**) is a flavor component found in a variety of essential oils.^[48] Galopin designed a short and economical synthesis of the natural



Scheme 10. Synthesis of roseophilin by Harrington and Tius. Bz = Benzoyl.

product, presumably to promote the use of *trans*-sabinene hydrate as a food additive.^[49] Treatment of isovaleraldehyde (**62**) generated dicarbonyl compound **64** in 82% yield (Scheme 11). A base-promoted aldol cyclization yielded cyclopentenone **65**. A subsequent Corey–Chaykovsky reaction and reduction with LiAlH_4 provided access to ($\pm$)-*trans*-sabinene hydrate (**66**) in 28% yield over four steps.

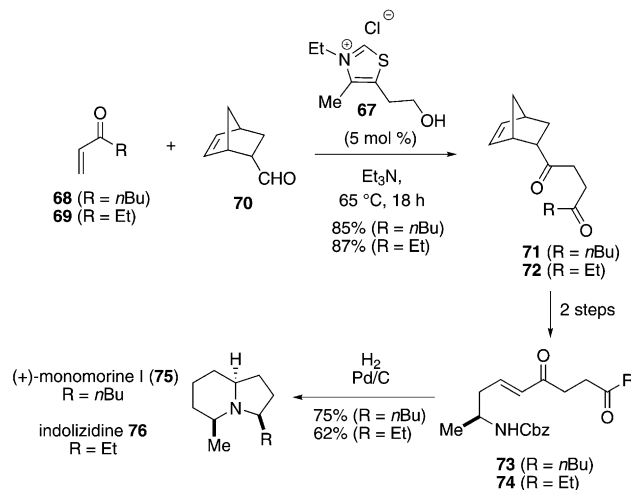


Scheme 11. Synthesis of ($\pm$)-*trans*-sabinene hydrate.

3.6. Synthesis of (+)-Monomorphine I and Related Natural Products

Indolizidine alkaloid (+)-monomorphine I (**75**) was isolated from the pharaoh ant *Monomorium pharaonis* L.,^[50] and (3*R*,5*S*,9*S*)-3-ethyl-5-methylindolizidine (**76**) was isolated from the venom of the ant *Solenopsis (Diplorhoptrum) conurata*.^[51] In 2003, Randl and Blechert reported the syntheses of these two compounds. Their approach involved

a five-step linear sequence featuring a sequential cross-metathesis and double reductive cyclization reaction as the key steps.^[52] The syntheses began with a thiazolium-catalyzed (**67**) intermolecular Stetter reaction between masked acrolein 5-norbornene-2-carbaldehyde (**70**) and vinyl ketone **68** or **69** to provide 1,4-diketones **71** and **72** (Scheme 12). A retro-Diels–Alder reaction to fragment the norbornene moiety,



Scheme 12. Synthesis of indolizidine alkaloids **75** and **76** by Randl and Blechert. Cbz = carbobenzyloxy.

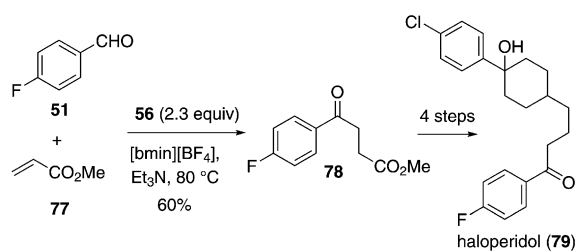
followed by an intermolecular cross-metathesis with a Cbz-protected (*S*)-4-penten-2-amine furnished carbamates **73** and **74**. The reductive amination of carbamates **73** and **74** gave natural products **75** and **76** in 35% and 29% overall yield, respectively.

3.7. Synthesis of Haloperidol

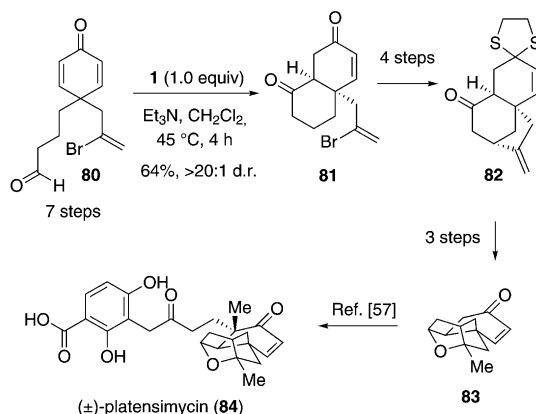
Haloperidol (**79**) is a widely used antipsychotic and its therapeutic properties have been historically associated with its D2 antagonist activity.^[53] In 2004, Grée and co-workers reported a synthesis of haloperidol (**79**) that relies on an efficient Umpolung approach. The 1,4-dicarbonyl compound **78** was obtained by a Stetter reaction between *p*-fluorobenzaldehyde (**51**) and methyl acrylate (**77**) catalyzed by the thiazolium salt **56** in an ionic liquid (Scheme 13). A subsequent four synthetic steps led to haloperidol in 30% overall yield.^[54]

3.8. Synthesis of (±)-Platensimycin

Platensimycin (**84**) has shown in vitro activity against *Staphylococcus aureus* and *Enterococcus faecium*.^[55] In 2007, Nicolaou and co-workers reported a formal synthesis of ($\pm$)-platensimycin,^[56] with key bond-forming reactions involving an intramolecular Stetter reaction, a tin-promoted radical cyclization, and a cyclization promoted by trifluoroacetic acid (Scheme 14). The exposure of ketoaldehyde **80** to 1.0 equiv-



Scheme 13. Synthesis of haloperidol (Haldol) by Grée and co-workers. Bmim = butylmethylimidazolium.

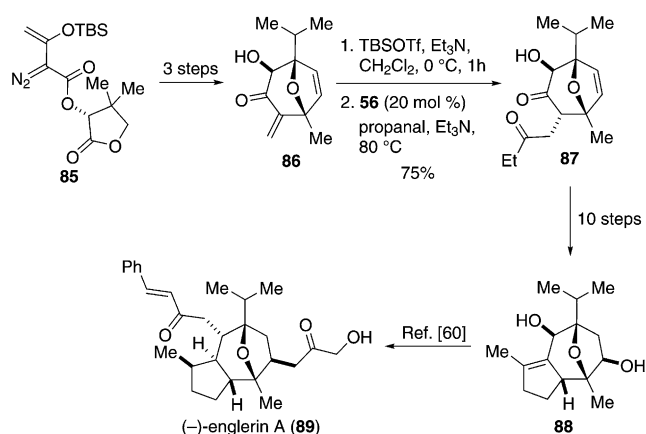


Scheme 14. Formal synthesis of (±)-platensimycin by Nicolaou et al. TFA = trifluoroacetic acid.

alents of azolium **1** and triethylamine provided the corresponding Stetter adduct **81** in 64 % yield with excellent diastereoselectivity (20:1 d.r.). Cyclohexenone **81** was converted into tetracycle **82** by formation of a dithiane from the enone and oxidation of the free ketone to the enone followed by a tin-radical cyclization. A subsequent three steps furnished the core structure of (±)-platensimycin (**83**).^[57]

3.9. Synthesis of Englerin A

Englerin A (**89**) is a guaiane-type sesquiterpene natural product isolated from the Tanzanian plant *Phyllanthus engleri* that has shown highly potent and selective cytotoxicity against various renal cancer cell lines at low nanomolar levels.^[58] In 2010, Theodorakis and co-workers reported an elegant enantioselective formal synthesis of englerin A (**89**) through a rhodium(II)-catalyzed [4+3] cycloaddition reaction between diazo ester **85** and 2-isopropyl-5-methylfuran to form the oxa-tricyclic motif of the structure and furnish α -hydroxyenone **86** in three steps.^[59] Simple protection of the secondary alcohol as the silyl ether followed by a Stetter reaction with propanal in the presence of thiazolium salt **56** gave diketone **87** as a single diastereoisomer in 75 % yield over two steps. A subsequent 10 steps furnished tricyclic substituted furan **88**, which is a known intermediate in the synthesis of englerin A by Ma and co-workers,^[60] in a 5 % yield over the 15 steps (Scheme 15).



Scheme 15. Formal synthesis of (–)-englerin A. KHMDS = potassium bis(trimethylsilyl)amide, TES = triethylsilyl.

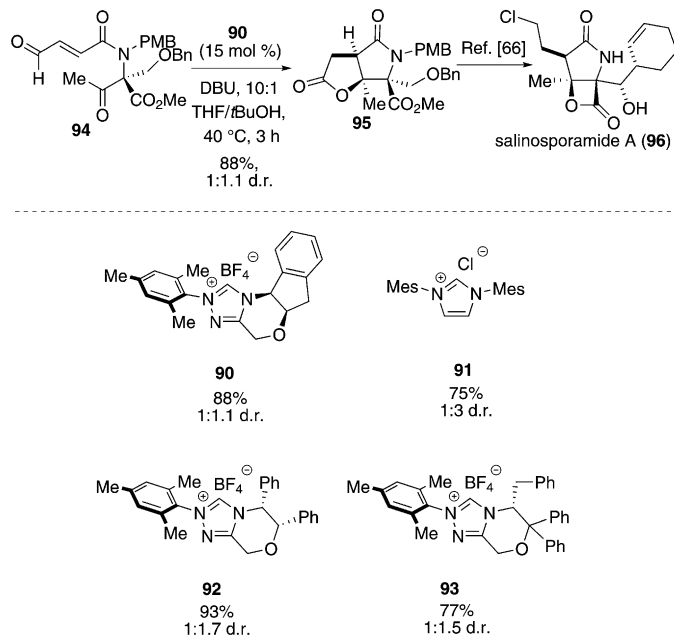
4. NHC-Homoenolate Equivalents

Homoenolates are synthetically important reactive species that can be used for the construction of both linear and cyclic structures. Although their enolate counterparts can be generated under a relatively large number of catalytic and stoichiometric conditions, there are relatively few general methods to generate homoenolates. Some early reported protocols for the generation of homoenolates require harsh conditions, which limited their synthetic use.^[61] In 2004, the research groups of Glorius and Bode independently reported the synthesis of γ -butyrolactones by the homoenolate annulation of aldehydes.^[62] This method relies on the catalytic generation of a homoenolate by using an NHC and an amine or alkoxide base. Since those initial reports, this area has undergone tremendous growth and has provided new methods for the highly selective assembly of important structural motifs.^[63]

4.1. Formal Synthesis of Salinosporamide A

Salinosporamide A (**96**) is a secondary metabolite isolated from the marine actinomycete bacteria and has attracted much attention because of its *in vitro* cytotoxic activity against several tumor cell lines, including HCT-116 human colon carcinoma ($IC_{50} = 1 \mu M$). Significant additional biological activity includes inhibition of the 20S proteasome and proteasomal chymotrypsin-like proteolytic activity ($IC_{50} = 1.3 nM$).^[64] In 2009, Struble and Bode reported a formal synthesis of salinosporamide through the formation of a γ -butyrolactone by an intramolecular homoenolate annulation of a ketone.^[65] This system suffered from many side reactions such as addition of the NHC-enolate or intramolecular aldol reactions. After extensive optimization, these side reactions were suppressed, but high diastereoselectivity was not achieved, even by the use of chiral NHC catalysts. Aldehyde **94** was synthesized in five steps from the reported chiral amine. The NHC reaction afforded the desired bicycle **95** in high yield, but with almost negligible diastereoselectivity. The NHC catalyst derived from azolium precursor **90** afforded the

best ratio of the desired diastereomer but in only an approximate 1:1 ratio (Scheme 16). The bicyclic lactone (**95**) is a known intermediate that has been converted into salinosporamide A in eight steps by Lam and co-workers.^[66]

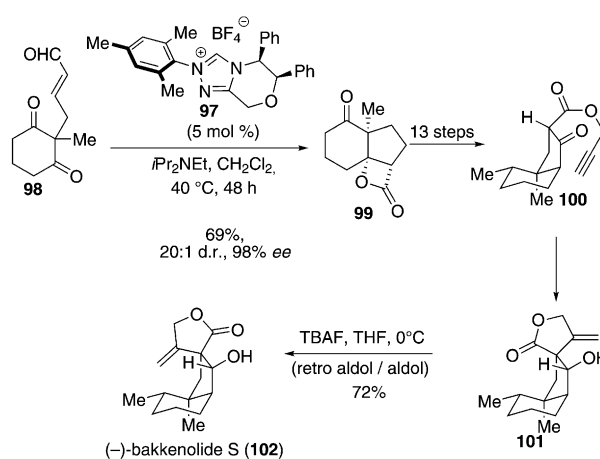


Scheme 16. Formal synthesis of salinosporamide A.

4.2. Synthesis of Bakkenolides I, J, and S

The first isolation of a bakkane was reported in 1968, and since then over 50 members of this family have been reported.^[67] Bakkanes are sesquiterpene natural products containing a *cis*-fused 5,6-bicyclic core with five contiguous stereocenters around the hydrindane core, including two quaternary carbon atoms and a spiro γ -butyrolactone.^[68] The bakkenolides have been shown to have antifeedant effects, inhibit platelet aggregation, and to have anticancer activity against a variety of tumor cell lines.^[69]

In 2010, our research group reported a highly diastereoselective and enantioselective NHC-catalyzed desymmetrization of 1,3-diketones.^[70] This method allowed the assembly of the indane core of bakkenolides, and was deployed as the key step in the synthesis of bakkenolides I, J, and S (Scheme 17). Aldehyde **98** was prepared in two steps from the corresponding diketone by a palladium-catalyzed Tsuji–Trost allylation and subsequent oxidation. Exposure of aldehyde **98** to chiral triazolium **97** and one equivalent of the Hunig base furnished lactone **99** in 69% yield with excellent diastereo- and enantioselectivity. Propargyl ester **100** was obtained in 13 steps from β -lactone **99**. A diastereoselective Mn(OAc)₃-promoted-formation of the spiro γ -butyrolactone furnished the undesired epimer **101** of bakkenolide S. A base-initiated retro-aldol/aldol process first reported by Depr s and co-workers^[71] allowed for the formation of bakkenolide S (**102**). The subsequent acylation with the corresponding acid chlorides led to the bakkenolides I and J. Thus, three natural

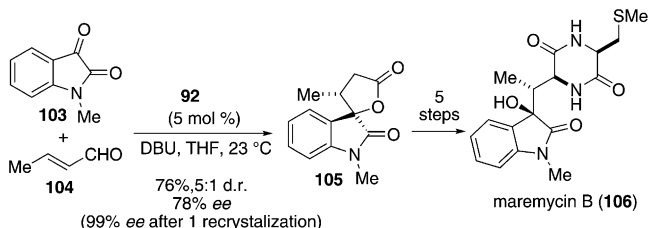


Scheme 17. Synthesis of bakkenolide S. TBAF = tetrabutylammonium fluoride.

products were synthesized in 20 steps in 2% overall yield, and this study represents the first completed syntheses using carbene-catalyzed homoenolate equivalents.

4.3. Synthesis of Maremycin B

Maremycin B (**106**) is a diketopiperazine alkaloid isolated from the culture broth of marine *Streptomyces* species B9173.^[72] In addition to its interesting structure, it has been shown to have anticancer activity. We recently reported the concise and enantioselective synthesis of maremycin B by employing an NHC-homoenolate equivalent addition (Scheme 18).^[73] The formation of a spirooxindole was accomplished by the homoenolate annulation of crotonaldehyde (**104**) and *N*-methylisatin (**103**). Lactone **105** was formed in 76% yield and good diastereo- and enantioselectivity, with the necessary enantiopure material obtained by a single recrystallization. A subsequent five-step sequence gave maremycin B (**106**) in 17% yield over six steps without the need for any protecting groups.



Scheme 18. Synthesis of maremycin B by an NHC-catalyzed formal [3+2] annulation

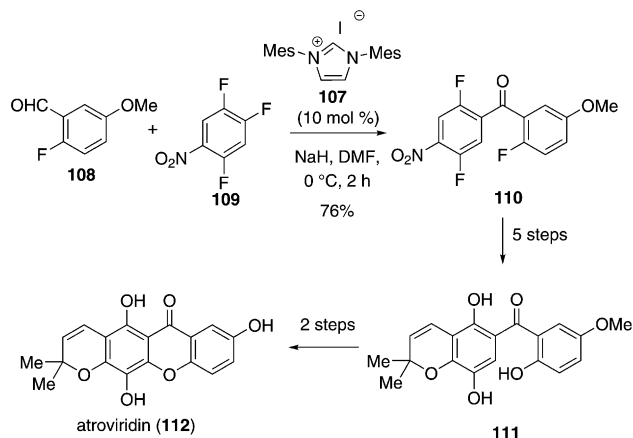
5. NHC-Catalyzed Aroylation Reactions

In 1990, Miyashita et al. reported the carbene-catalyzed nucleophilic aroylation of 4-chloro-1*H*-pyrazolo-[3,4-*d*]pyrimidines.^[74] This reaction employs a NHC-generated acyl anion as the nucleophile in nucleophilic aromatic

substitution reactions. Over the past 20 years, Miyashita, Suzuki, and co-workers have developed this reaction into a general method for the synthesis of aroyl compounds.^[75] In 2008, they reported the aroylation of functionalized fluoro-benzenes with NHC catalyst loadings as low as 1 mol %.^[76]

5.1. Synthesis of Atroviridin

Atroviridin (**112**) is an oxygenated xanthone isolated from *Garcinia atroviridis* Griff.^[77] Recently, Suzuki et al. reported the total synthesis of atroviridin by using his NHC-catalyzed aroylation strategy to assemble the tetracyclic core (Scheme 19).^[75e] The treatment of functionalized benzaldehyde **108** and substituted benzene ring **109** with 10 mol % of catalyst **107** and NaH yielded benzophenone **110** in 76 % yield which was subsequently converted into triphenol **111** in five steps. A subsequent MnO₂ oxidation, followed by an intramolecular Michael addition reaction and demethylation with boron tribromide gave atroviridin in nine steps with a 14 % overall yield.



Scheme 19. Synthesis of atroviridin by Suzuki et al.

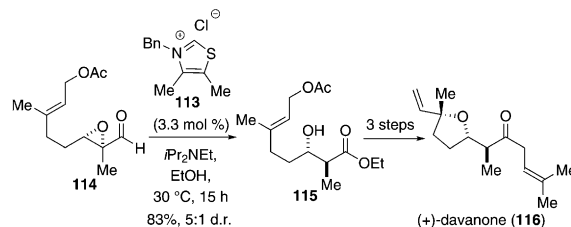
6. NHC-Catalyzed Redox and Oxidative Processes

In addition to the various Umpolung reactions catalyzed by NHCs (e.g., benzoin, Stetter, and homoenolate equivalents), these unusual Lewis bases are also capable of promoting redox (internal or external) reactions involving terminal acylation events.^[1c,d,78] Reports by our research group^[79] and by Studer and co-workers^[80] have demonstrated that the oxidation of the activated alcohol intermediate with metal or organic oxidants allows for the direct conversion of unactivated aldehydes into the corresponding esters. Aldehydes with an α -substituent (e.g., chlorides) have also been employed in this redox process.^[81] In addition to esters, other functionalities such as amides^[82] and acyl azides^[83] have been obtained by this redox NHC method. In addition to these aldehyde-based transformations, Lupton and co-workers reported the first conjugate addition of α,β -unsaturated acyl azoliums.^[84] These intermediates have been shown to be excellent conjugate acceptors.^[85] These non-Umpolung type

of reaction manifolds have added greatly to the synthetic repertoire of carbene catalysis, and new applications of these processes are just now emerging. This section includes reports of total and formal syntheses completed by using NHC catalysis for these non-Umpolung transformations.^[86]

6.1. Synthesis of (+)-Davanone

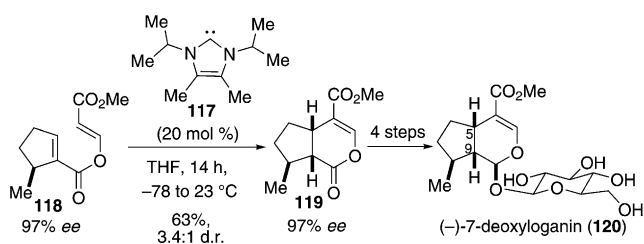
Davanone (**116**), is a sesquiterpene natural product which exhibits antifungal and antispasmodic activity. It was first isolated from *Artemisia pallens* in 1968, and is the principle component of davana oil.^[87] In 2009, Vosburg and co-workers reported a short total synthesis of (+)-davanone involving an epoxide-opening NHC reaction (Scheme 20).^[88] The treatment of α,β -epoxyaldehyde **114** with the thiazolium salt **113** and Hunig's base triggered an epoxide opening/esterification to afford *anti* diastereomer **115** in good yield. A palladium-catalyzed allylic O-alkylation, formation of the Weinreb amide, and Grignard addition furnished (+)-davanone (**116**) in only seven steps from geranyl acetate.



Scheme 20. Total synthesis of (+)-davanone by Vosburg and co-workers.

6.2. Synthesis of (–)-7-Deoxyloganin

(–)-7-Deoxyloganin (**120**) is a monoterpenoid iridoid, and the majority of these monoterpenoid natural products contain a *cis* relationship between H5 and H9 in the cyclopentapyran core (Scheme 21).^[89] These iridoid natural products exhibit broad biological activity and are key intermediates in alkaloid biosynthesis.^[90] Candish and Lupton recently reported the synthesis of (–)-7-deoxyloganin (**120**) through an interesting NHC-catalyzed reaction. In this reaction, free carbene **117** is used as a nucleophilic catalyst to promote the α,β -unsaturated enol ester rearrangement of **118** to form dihydropyranone **119**.^[91] Surprisingly, this reaction proceeds in the presence of the methyl ester, even though NHCs are known to activate esters for transesterification.^[92] The α,β -unsaturated enol ester **118** was synthesized from 2,5-dimethoxytetrahydrofuran in 13 steps. NHC **117** was identified as the optimal catalyst in terms of the yield and selectivity of the α,β -unsaturated enol ester rearrangement. Four subsequent steps gave (–)-7-deoxyloganin (**120**) in 18 steps and 0.7 % overall yield. In 2011, Candish and Lupton reported a modified synthesis starting from (*S*)-citronellal. This route allowed access to (–)-7-deoxyloganin (**120**) in just ten steps with 3.1 % overall yield.^[93] A well-designed and executed crossover study

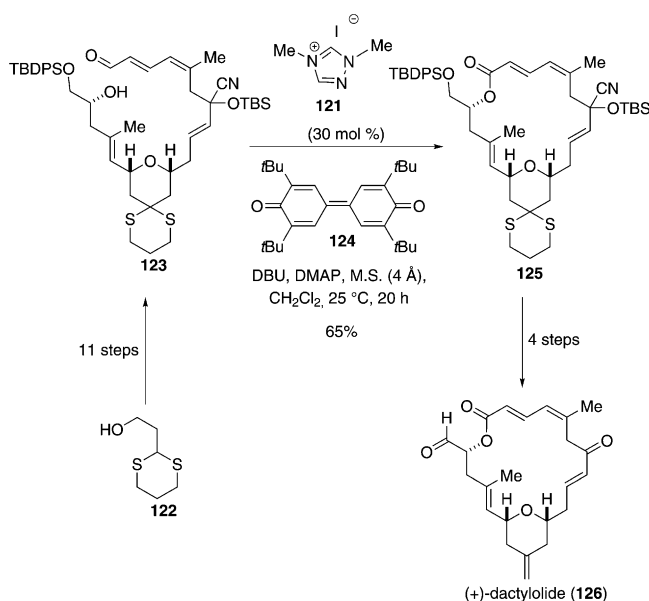


Scheme 21. Synthesis of (–)-7-deoxyloganin by Candish and Lupton.

revealed that this reaction likely proceeds in an intramolecular manner.^[93]

6.3. Synthesis of (+)-Dactylolide

(+)-Dactylolide (**126**) is a cytotoxic 20-membered macrocycle isolated from the Vanuatu sponge *Dactylospongia* sp. which displays modest inhibitory activities towards tumor cell growth in leukemia and ovarian cancer cell lines.^[94] Hong and co-workers have very recently reported a total synthesis of (+)-dactylolide (Scheme 22). The synthesis showcased



Scheme 22. NHC-catalyzed macrolactonization towards dactylolide. DMAP = 4-dimethylaminopyridine.

a NHC-catalyzed oxidative macrolactonization reaction to form the 20-membered macrocycle.^[95] An 11-step reaction sequence converted 1,3-dithiane-2-ethanol (**122**) into ω-hydroxy aldehyde **123**. Aldehyde **123** underwent an impressive intramolecular oxidative macrolactonization to afford 20-membered lactone **125** in 65% yield. The optimal conditions employed for this macrocyclization were azolium **121**, DMAP, and 3,3',5,5'-tetra-*tert*-butyldiphenylquinone (**124**).^[96] These reagents are an integration of earlier independent NHC oxidation methods by the research groups of Scheidt^[97] and Studer.^[80] This transformation is the first example of an NHC-

catalyzed oxidative macrolactonization of ω-hydroxy aldehydes. Four additional steps provided (+)-dactylolide (**126**) in 16 steps with 1.9% overall yield.

7. Summary

Carbene catalysis is a rapidly expanding field that has greatly added to the arsenal of efficient and stereoselective bond-forming reactions over the last decade. This Minireview presents the current examples of benzoin condensations, Stetter reactions, homoenolate reactions, and nucleophilic catalyst reactions that can be used to access complex targets. NHC-catalyzed processes are highly versatile in terms of the different reactivity patterns that can be accessed (Umpolung, enolate, oxidation manifolds), and this organocatalytic strategy has come far since its biomimetic beginnings with pyruvate decarboxylase and Ugai et al. in the early 1940s. The further exploration of NHC catalysis will undoubtedly fuel the continued discovery of new methods and reactions, with future subsequent applications in total synthesis. Further research and focus in this exciting area will undoubtedly lead to additional strategies for the construction of privileged motifs, which will be of great value to the fields of natural products total synthesis and medicine.

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