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Dienals Derived from Pyridinium Salts and Their Subsequent Application in Natural Product Synthesis

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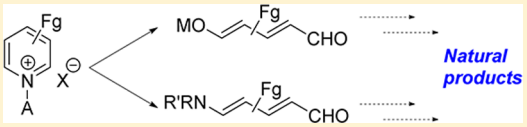
ABSTRACT: Transformation of quaternary pyridinium compounds into functionalized conjugated dienes can be adapted to natural product synthesis with great effect. Most conspicuously, the transformation has been employed in the preparation of polyenic structures. However, in a more convoluted application, polycyclic systems have arisen from elaboration of the diene motif. The goal of the present account is to survey the utility of dienals derived from pyridinium salts as the means to establish molecular architecture featured in natural products.



Pyridines carrying a formal positive charge on the nitrogen atom can undergo nucleophilic addition to the adjacent position and subsequent ring-opening through an apparent disrotatory electrocyclic mechanism.[1] Thus, in this case, disruption of the aromatic π-system will lead to the formation of functionalized conjugated dienes. Considering the variations possible, in terms of functional pattern on the pyridinium salt and the types of nucleophiles available, the transformation represents a powerful strategy to manufacture five-carbon units containing a dienal moiety.

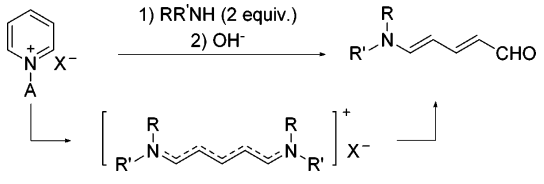
At the start of the 20th century, Zincke and König independently reported how treatment of a pyridinium salt with selected amines resulted in the formation of ring-opened products.[2,3] In a following communication, Zincke established the preparation of 5-aminopenta-2,4-dienals.[2d] Two decades later, Baumgarten then demonstrated that the reaction of pyridine sulfur trioxide complex with lye afforded the sodium salt of 5-hydroxypenta-2,4-dienal.[4] Consequently, when taken together, these early results pointed toward a more general utility of quaternary pyridinium compounds as synthetic precursors in organic chemistry.[5,6]

5-Aminopenta-2,4-dienals: Synthetic Manipulation and Application. In its most fundamental form, reacting a pyridinium salt with 2 equivalents of a secondary amine will result in the corresponding 5-aminopenta-2,4-dienal upon basic hydrolysis (Scheme 1).[2d] The compounds formed in this manner are commonly referred to as Zincke aldehydes. The secondary amine need not be symmetric and can incorporate a number of functional patterns.

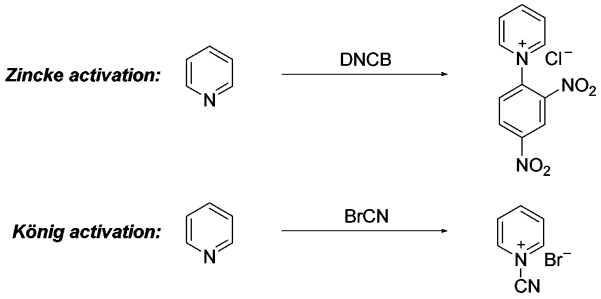
The impetus of the transformation is derived from the appendage on the quaternary nitrogen. However, as its sole purpose is to activate the pyridine scaffold, it will be excised during product formation. The manner of activation generally adheres to the original protocols developed by Zincke or König, respectively (Scheme 2).[2,3] In the first case, nucleophilic attack is promoted through facile *N*-arylation with 1-chloro-2,4-dinitrobenzene (DNCB).[7,8] In the second case, the same process is enabled by transient *N*-cyanation with cyanogen bromide.[3,9]

Adding one or more substituents to the pyridine scaffold may in principle render the ring-opening regiochemically ambiguous, unless a mirror plane exists. Nevertheless, it is found that pyridinium salts functionalized in the 3-position preferentially give rise to the corresponding 2-substituted Zincke aldehydes (Scheme 3).[10]

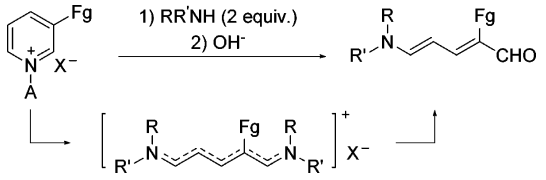
Scheme 1. Preparation of Zincke Aldehydes



Scheme 2. Methods of Activation



Scheme 3. Ring-Opening of 3-Substituted Pyridinium Salts



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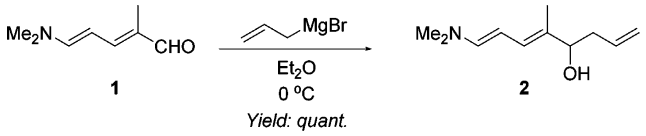
By nature, the Zincke aldehydes are ambident electrophiles, capable of undergoing addition to both ends of the conjugated system. However, as a masked dialdehyde, the functional groups are orthogonal and may be expected to exhibit different reactivity toward nucleophiles. Thus, by analogy with α,β-unsaturated aldehydes,[11] it is anticipated that "hard" nucleophiles add to the aldehyde moiety, while "soft" nucleophiles add at the opposite aspect containing the amino terminus. As the amine function in theory can act as a leaving group, addition at the 5-position is followed by a presumed 1,6-elimination mechanism, resulting in an overall substitution.

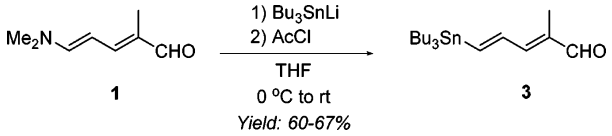
To illustrate this regioselective idiosyncrasy of 5-aminopenta-2,4-dienals, reaction of Zincke aldehyde **1** with allylmagnesium bromide takes place via 1,2-addition to provide the corresponding homoallylic alcohol **2** (Scheme 4).[12]

Scheme 4. Direct Addition to a Zincke Aldehyde



However, when the same Zincke aldehyde **1** is treated with (tributylstannyl)lithium, followed by an excess of methyl iodide or acetyl chloride, the overall sequence produces the corresponding 5-(tributylstannyl)penta-2,4-dienal (**3**) (Scheme 5).[13] The necessity of having an alkylating or acylating agent

Scheme 5. Conjugate Addition to a Zincke Aldehyde

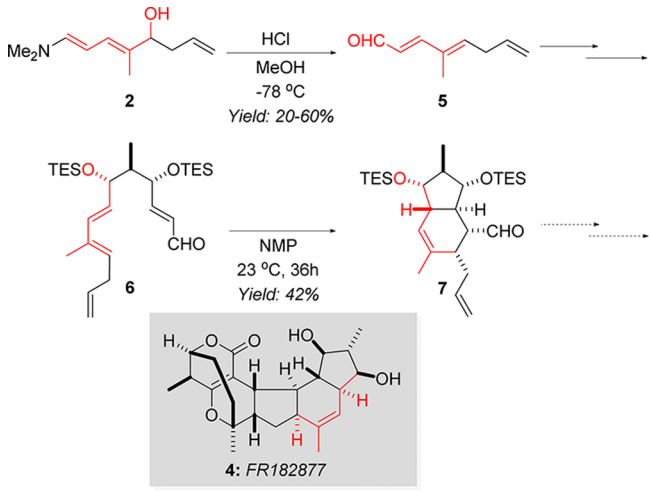


present to bring about the reaction suggests that, while the initial 1,6-addition may be proficient, the subsequent 1,6-elimination only proceeds once the amine function is converted to a compatible leaving group.

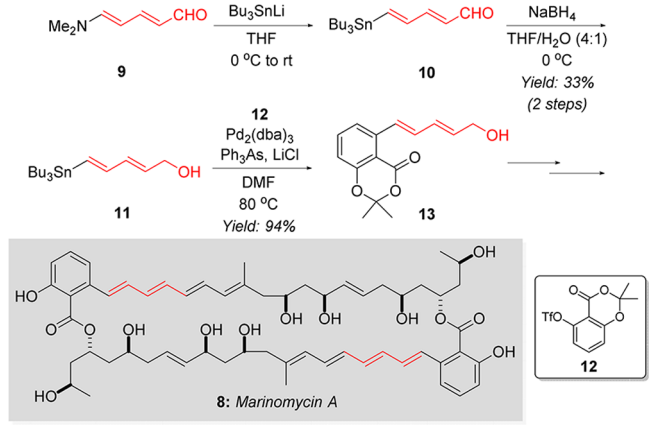
The orthogonal reactivity of Zincke aldehydes has been exploited in total synthesis. For example, Sorensen and co-workers opted for the 1,2-addition described in Scheme 4 as they embarked on their first approach toward the microtubule-stabilizing agent FR182877 (**4**) (Scheme 6).[14] Careful acidic hydrolysis of the doubly vinylogous aminal **2** afforded the transposed all-*E* 2,4,7-trienal **5**. With further iteration on the unmasked aldehyde via asymmetric Evans aldol condensation and subsequent elaboration, they prepared an all-*E* 2,4,7,12-tetraenal **6**, which was set up for an intramolecular Diels–Alder reaction. Although arriving at the key hydrindene aldehyde **7**, the inability to control olefin geometry in a later step terminated the effort.

A more successful implementation of Zincke chemistry in total synthesis has been demonstrated by Evans and co-workers.[15] While highlighting the use of 1,6-addition/elimination on Zincke aldehydes, it also exhibits umpolung as a strategic device. In their endeavor to prepare marinomycin A (**8**), a 44-membered macrolide polyene–polyol antibiotic, the introduction of unsaturation in the linear backbone was negotiated by taking advantage of 5-(tributylstannyl)penta-2,4-dienal (**10**) (Scheme 7). After reduction of the aldehyde

Scheme 6. Synthesis Directed toward (+)-FR182877



Scheme 7. Synthesis of Marinomycin A

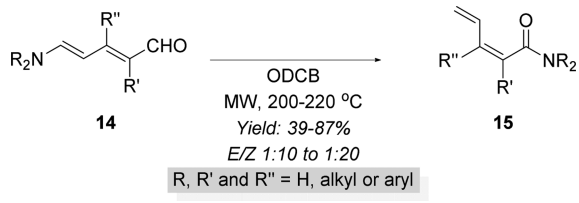


moiety, the resulting 5-(tributylstannyl)penta-2,4-dien-1-ol (**11**) was subjected to Stille coupling with aryl triflate **12**. The complete synthesis of marinomycin A (**8**) was executed in a triply convergent 18-step sequence (longest linear sequence) in an impressive overall yield of 3.5%.

A different aspect relating to the Zincke aldehydes, simultaneously involving both functionalities, is the efficient amine transposition disclosed by Vanderwal and co-workers.[16] When subjected to heat under microwave conditions in 1,2-dichlorobenzene (ODCB), a series of 5-aminopenta-2,4-dienals **14** was converted in a highly stereocontrolled manner to the corresponding *Z*-penta-2,4-dienamides **15** (Scheme 8).

On the basis of computational methods and experimental work, a mechanistic proposal has been put forth, suggesting a pericyclic cascade for the thermal rearrangement.[16b] The mechanism involves ketene formation via a [1,5]-hydride

Scheme 8. Rearrangement of Zincke Aldehydes



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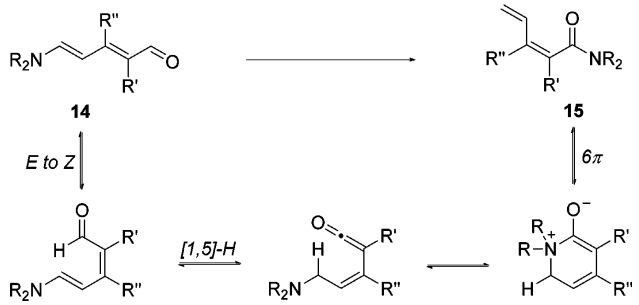
shift, followed by ring-closure by the amine onto the ketene and, finally, 6π-electrocyclic reversion to generate the transposed product (Scheme 9).

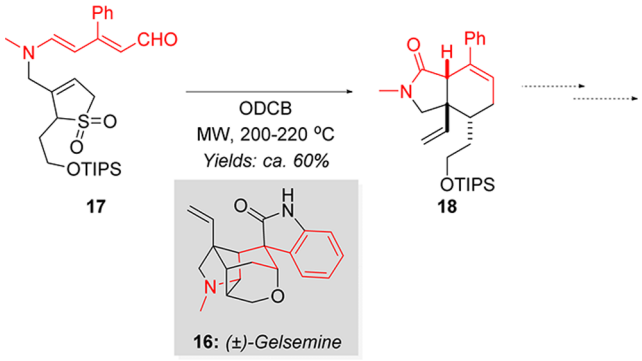
Scheme 9. Proposed Mechanism for Rearrangement of Zincke Aldehydes



The use of Zincke aldehydes in aliphatic chemistry necessitates expulsion of the secondary amine; i.e., its role is limited to act as a functional handle. Yet the role may be recast when applied to the construction of heterocyclic systems. Secondary amines incorporating a reactive pattern can interact with the penta-2,4-dienal moiety in an intramolecular manner. Capitalizing on the rearrangement of Zincke aldehydes, Vanderwal and co-workers have demonstrated its value in the construction of complex scaffolds found in natural products.[17]

In an approach to the preparation of spirooxindole alkaloid (±)-gelsemine (**16**), Vanderwal and co-workers implemented the cascade of transposition/cycloaddition (Scheme 10).[18]

Scheme 10. Synthesis Directed toward (±)-Gelsemine

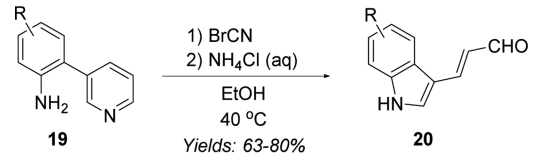


Although ultimately failing to achieve the spirocyclic compound, the synthetic endeavors display an impressive array of pericyclic transformations, staging Zincke aldehyde **17** as the pivotal feature.

The Vanderwal group has been a central proponent in the exploration and application of Zincke aldehydes as the means to prepare complex natural products.[19] In particular, their attention to members of the strychnos, aspidosperma, and iboga alkaloids has spawned highly efficient total syntheses through identification of the pyridinium retron as a strategic hinge for intramolecular Diels–Alder reaction.[20,21]

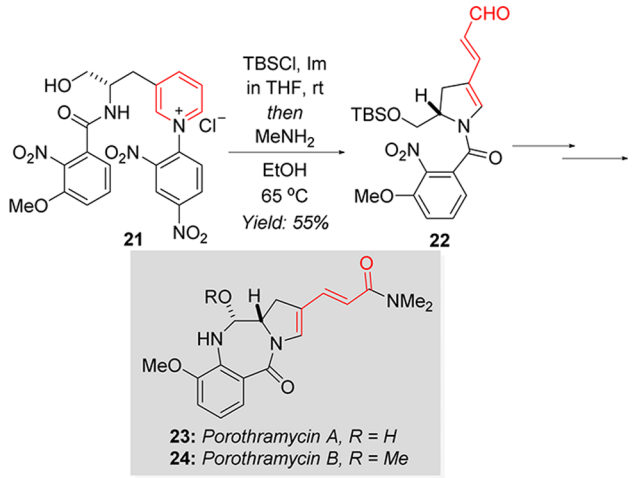
The intermolecular reaction with primary amines does not lead to formal ring-opening of pyridinium salts but rather gives rise to exchange of the *N*-substituent via an ANRORC mechanism.[6a,b] However, in the case of an intramolecular reaction, when the pyridinium salt is tethered with a primary amine in the 3-position, ring-opening proceeds smoothly. For example, when 2-(pyridin-3-yl)anilines **19** are activated according to the König protocol with cyanogen bromide, the corresponding indole-3-propenals **20** are produced in good yields after hydrolytic workup (Scheme 11).[9]

Scheme 11. Intramolecular Ring-Opening of Tethered Pyridinium Salts



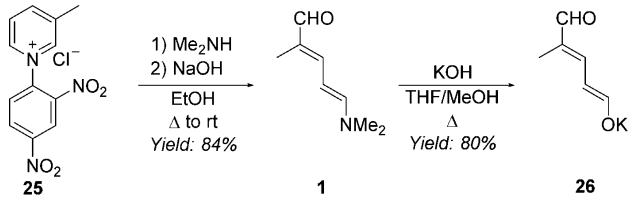
Fascinatingly, even pyridinium salts tethered at the 3-postion with amides can be encouraged to undergo ring-opening. Again, Vanderwal and co-workers have disclosed an efficient approach to natural product synthesis, leading to the formal syntheses of pyrrolobenzodiazepinone antitumor antibiotics porothramycin A (**23**) and B (**24**) (Scheme 12).[22]

Scheme 12. Enantioselective Total Synthesis of Porothramycin A and B



The domain between Zincke aldehydes and 5-hydroxypenta-2,4-dienal salts is arbitrary and overlapping, as the one can give rise to the other. Thus, when Zincke aldehyde **1** is reacted with potassium hydroxide in a suitable solvent, the corresponding 5-hydroxypenta-2,4-dienal salt **26** can be isolated (Scheme 13).[23a] Although the ring-opening of 3-substituted pyridinium salts to Zincke aldehydes generally occurs with a pronounced degree of regioselectivity, subsequent formation of the 5-hydroxypenta-2,4-dienal salts eradicates any ambiguity.

Scheme 13. Conversion of a Zincke Aldehyde to 5-Hydroxypenta-2,4-dienal Salt



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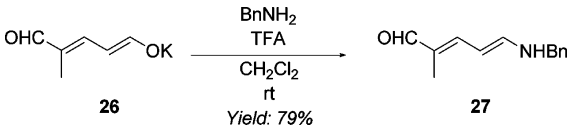
The significance of this transformation is borne out when a 2-substituted 5-hydroxypenta-2,4-dienal potassium salt **26** is reacted with an amine (Scheme 14).[23a,b] First, it is apparent

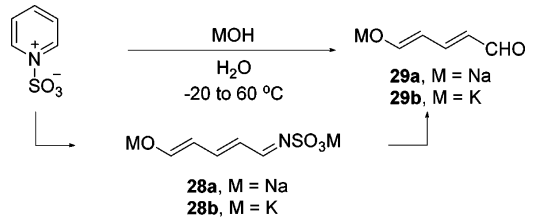
Scheme 14. Conversion of a 5-Hydroxypenta-2,4-dienal Salt with Primary Amine



that the 2-substituted 5-aminopenta-2,4-dienal **27** is greatly preferred. Second, reaction with primary amines on 5-hydroxypenta-2,4-dienal potassium salts affords 5-aminopenta-2,4-dienals not accessible with the Zincke protocol.[23c]

5-Hydroxypenta-2,4-dienal Salts: Synthetic Manipulation and Application. When pyridine sulfur trioxide complex is treated with an alkali base at subzero temperatures, swift ring-opening ensues to afford a dialkali salt of 5-hydroxypenta-2,4-dienal iminosulfonate **28**. Gradually warming the dialkali salt **28** in basic media effects further hydrolysis, to produce the corresponding 5-hydroxypenta-2,4-dienal salt **29** (Scheme 15).[4,24] The original protocol of Baumgarten pertains

Scheme 15. Preparation of 5-Hydroxypenta-2,4-dienal Salts



to the sodium salt **29a**, prepared over two steps in a good overall yield.[4c] It is, however, more conveniently produced in a one-pot procedure, without any substantial loss of product.[24] Both the sodium and potassium salts of 5-hydroxypenta-2,4-dienal **29** are formed with equal ease. Yet, the physical behavior of the two salts is dissimilar with respect to hydration of water. Thus, while the sodium salt **29a** retains water, the potassium salt **29b** can be obtained water-free. This has some practical implications for the subsequent chemistry to be performed, as in some instances the presence of water may be detrimental to the outcome. Not surprisingly, neither the sodium nor the potassium salt **29** is particularly soluble in nonpolar solvents. To improve solubility, the counterion may be exchanged to form a tetrabutylammonium salt.[24] The parent 5-hydroxypenta-2,4-dienal **30** can also be obtained as a methanolic solution at −70 °C by neutralizing the hydrate sodium salt **29a** with carbon dioxide, although even at low temperatures the compound is prone to decomposition.[6c]

5-Hydroxypenta-2,4-dienal (**30**) is formally an enol tautomer of pent-2-enedial (**30**) and is trivially referred to as glutaconaldehyde (**30**), signifying the structural relationship to glutaconic acid (**31**) (Figure 1). The trivial name is

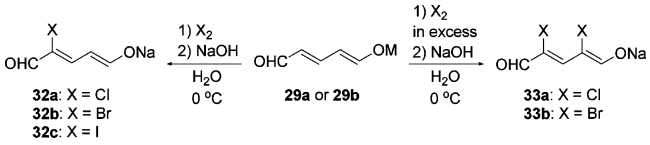
Figure 1. Structural relationship.

somewhat misleading, as it does not indicate the extensive prototropic delocalization conferred on the nominal dialdehyde by the interlinked functional pattern, which gives the system its unique reactivity.

In contrast to the Zincke aldehydes described in the previous section, glutaconaldehyde salts are ambident nucleophiles by virtue of the formal negative charge residing within the conjugated structure. It is therefore expected that reaction with "hard" electrophiles occurs at the alkoxide moiety, while reaction with "soft" electrophiles takes place at the flanking carbon atom.[25]

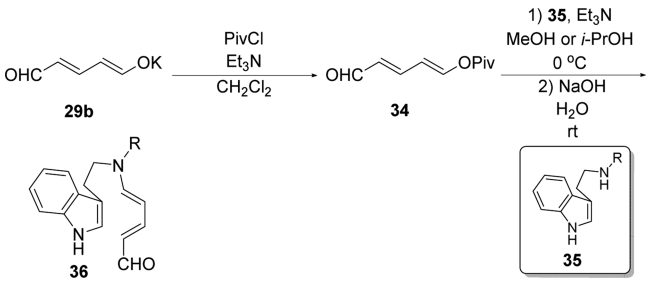
Functionalization of the glutaconaldehyde scaffold, through exploration of classic enolate chemistry with "soft" electrophiles, has been very limited and has found no application in natural product synthesis.[4b,26,27] However, early on, Baumgarten recognized the reactive pattern that is peculiar to glutaconaldehyde salts. Treating the sodium salt **29a** with elemental halogen was surmised to give rise to the correspondingly 2-halogenated compounds **32**.[4b] Becher and co-workers later revisited the experiments and corroborated the findings by making the 2-chloro, 2-bromo, and 2-iodo congeners **32a**, **32b**, and **32c** (Scheme 16).[26] Moreover, they selectively prepared the sodium salts of 2,4-dichloro- and 2,4-dibromoglutacon aldehyde **33a** and **33b**, respectively.

Scheme 16. Halogenation of Glutaconaldehyde Salts



The constellation between a "hard" electrophile and a glutaconaldehyde salt already appears in the seminal work by Baumgarten, as exemplified by the reaction with benzoyl chloride.[4b] As the presence of a formal negative charge within the glutaconaldehyde scaffold dictates its chemistry and precludes most reactions, the purpose is rather to convert the alkoxide into a suitable nucleofuge, whereby the innate electrophilic nature of the conjugated system can be harvested. In the supporting information accompanying the synthetic endeavors within the strychnos family, based on tryptamine derived Zincke aldehydes, Vanderwal and co-workers outline just such an approach (Scheme 17).[28] Treating the glutaconaldehyde potassium salt **29b** with pivaloyl chloride affords the corresponding pivalate **34**, which is subsequently reacted with tryptamine **35** in a 1,6-addition/elimination process.

Scheme 17. Acylation of Glutaconaldehyde Salts and Synthetic Utility



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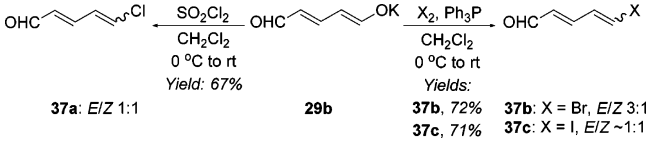
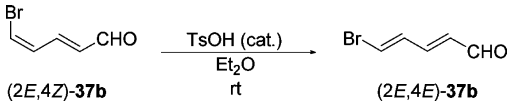
In terms of synthetic application, by far the most useful transformation of glutaconaldehyde salts is the functional interconversion from alkoxide to halogen, which provides the corresponding 5-halopenta-2,4-dienals. Combining elemental halogen with triphenylphosphine creates a highly oxophilic halophosphonium halide which reacts promptly with alkoxides.[29] While the reaction is related to the Appel protocol,[30] it differs mechanistically. The halogenation cannot be the result of a S_N2 substitution, but rather a 1,6-addition/elimination process, brought about by an attack of the halide ion on the conjugated system and facilitated by the formation of triphenylphosphine oxide. Duhamel and co-workers have developed a protocol along these lines, treating the water-free potassium salt **29b** with halophosphonium halides obtained from either bromine or iodine. This affords the corresponding 5-bromo- or 5-iodopenta-2,4-dienals **37b** or **37c** in good yields, as a separable mixture of their respective (2*E*,4*E*)- and (2*E*,4*Z*)-isomers (Scheme 18).[31] Using a different reagent, Duhamel also prepared the 5-chloropenta-2,4-dienal **37a** by reacting the potassium salt **29b** with thionyl chloride.

Scheme 18. Preparation of 5-Halo-2,4-dienals



The (2*E*,4*E*)- and (2*E*,4*Z*)-mixture of 5-bromopenta-2,4-dienal **37b** can be separated chromatographically or by crystallization.[31] However, Duhamel and co-workers have described a convenient procedure, which allows the preparation of pure (2*E*,4*E*)-**37b** via acid-catalyzed isomerization (Scheme 19).[32]

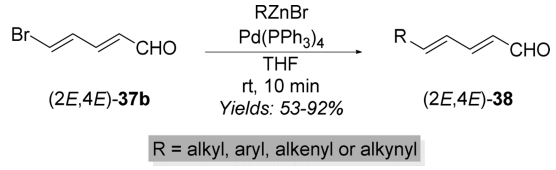
Scheme 19. Isomerization of 5-Bromopenta-2,4-dienal



Recasting the electronics of the glutaconaldehyde scaffold via halo deoxygenation enables iterative functionalization of the orthogonal substituents and renders the 2,4-dienal motif a viable synthon in strategic planning. Transition-metal-catalyzed cross-coupling on vinylic halides is well established and offers a plethora of alternative methods to execute C−C bond formation.[33] Several of these methods have been applied in the augmentation of the 2,4-dienal backbone by substitution of the appended halogen in the 5-position. Reflecting the intrinsic reactivity, the transformations have generally been limited to cross-coupling on the 5-bromo- and 5-iodopenta-2,4-dienals **37b** and **37c**, with the former being more frequently used.

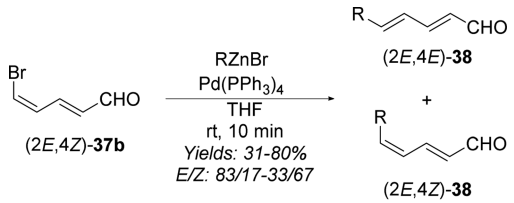
Palladium-catalyzed cross-coupling on (2*E*,4*E*)-**37b** proceeds rapidly at room temperature with a variety of zinc reagents to afford the corresponding 5-substituted (2*E*,4*E*)-dienals **38** in good yields (Scheme 20).[32,34] The functional tolerance is generally high, as both alkyl-, aryl-, vinyl-, and alkynylzinc reagents react in the presence of the aldehyde group without any accompanying 1,2-addition. The exception is Reformatsky reagents, which add directly to the aldehyde in preference to cross-coupling.[34]

Scheme 20. Cross-Coupling on (2*E*,4*E*)-5-Bromopenta-2,4-dienal



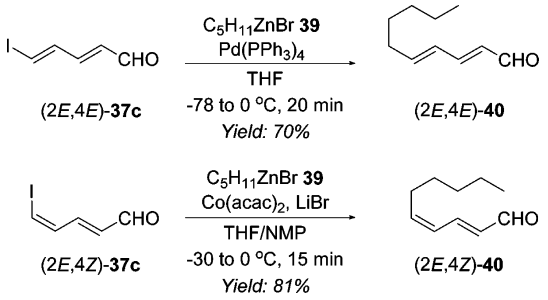
Contrary to the palladium-catalyzed cross-coupling on (2*E*,4*E*)-**37b**, the integrity of the olefin geometry is compromised when (2*E*,4*Z*)-**37b** is reacted under the same conditions (Scheme 21).[34] Thus, in this case, the cross-coupling between (2*E*,4*Z*)-**37b** and zinc reagents affords a mixture of geometric products **38**, favoring the (2*E*,4*E*)-isomer **38**. Plé and co-workers have suggested a mechanism, whereby the initially formed 5-substituted (2*E*,4*Z*)-dienal **38** is scrambled by the combined association/dissociation of $ZnBr_2$ and Pd(0)-complex. Lewis acidic $ZnBr_2$ coordinates to the aldehyde, causing the nucleophilic Pd(0)-complex to attack in a conjugated manner. The resulting π-allyl complex can switch between *syn*- and *anti*-geometry through $\pi-\sigma-\pi$ equilibration, leading to double bond isomerization.

Scheme 21. Cross-Coupling on (2*E*,4*Z*)-5-Bromopenta-2,4-dienal



In conjunction with some investigations on naturally occurring deca-2,4-dienals (2*E*,4*E*)-**40a** and (2*E*,4*Z*)-**40b**, isolated from the diatom *Thalassiosira rotula*, Pohnert and co-workers subjected both 5-iodopenta-2,4-dienal (2*E*,4*E*)-**37c** and (2*E*,4*Z*)-**37c** to cross-coupling with the zinc reagent **39** (Scheme 22).[35] Not surprisingly, the palladium catalyzed reaction of (2*E*,4*E*)-**37c** proceeded to afford the (2*E*,4*E*)-deca-2,4-dienal **40a**. However, in contrast to what is described above, the cobalt catalyzed reaction of (2*E*,4*Z*)-**37c** only gave (2*E*,4*Z*)-deca-2,4-dienal **40b**. It is therefore possible to retain the (2*E*,4*Z*)-geometry of a 5-halopentadienal in cross-coupling by the judicious choice of catalyst.

Scheme 22. Syntheses of Naturally Occurring Deca-2,4-dienals



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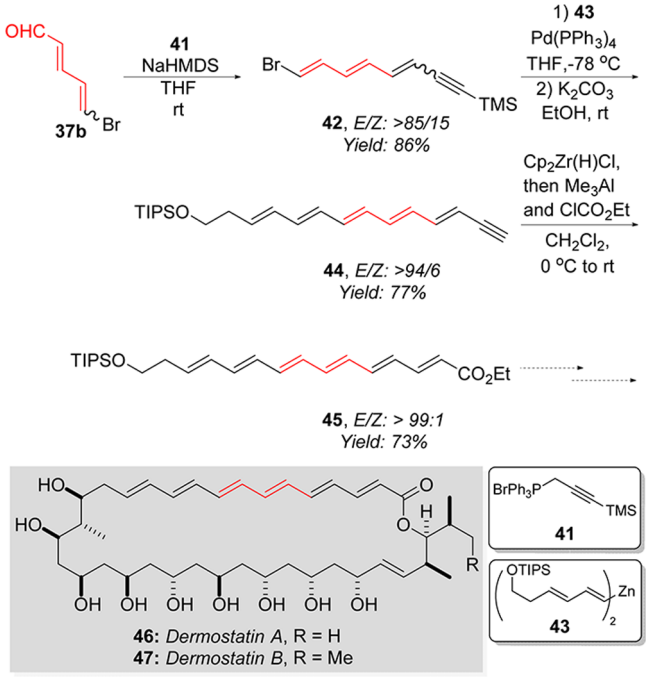
Despite this, although Negishi coupling of 5-halopentadienals can be executed without accompanying 1,2-addition, there is an apparent preference for synthetic manipulation of the aldehyde group prior to functionalization of the 5-position. This is explainable in view of the Michael accepting characteristics of the conjugated system, which makes the double bond susceptible to acid catalyzed isomerization. Duhamel and co-workers have reported the conversion of geometrically pure **37b** into a thermodynamic mixture of isomers in hydrated chloroform.[32] Reacting the aldehyde portion in a way that disrupts the Michael acceptor motif will confer configurational stability on the diene in subsequent manipulations.

Exploring the all-*E*-conjugated pattern common to oxo polyene macrolide antibiotics, Lipshutz and co-workers have developed an approach toward preparation of tetra-, penta-, and hexaenes, performing sequential elaboration of (2*E*,4*E*)-**37b**.[36] Accordingly, subjecting an isomeric mixture of **37b** to an *E*-selective Wittig reaction with phosphonium bromide **41**, followed by cross-coupling with alkenyl zinc reagent **43**, gave the all-*E* 3,5,7,9,11-pentaen-1-yne **44** (Scheme 23). Further

Scheme 23. Polyene Iteration toward Macrolides

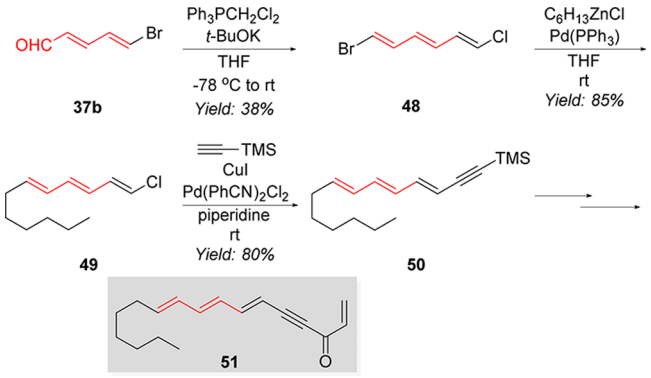


elaboration of the alkyne moiety via hydrofunctionalization resulted in the all-*E* 2,4,6,8,10,12-hexaenoic acid ester **45** constituting the oxo polyenic structure found in dermostatin A (**46**) and dermostatin B (**47**).

Also taking advantage of (2*E*,4*E*)-**37b** as a polyene precursor, Ramondenc and co-workers performed a Wittig reaction to obtain the orthogonal (1*E*,3*E*,5*E*)-1-bromo-6-chlorohexa-1,3,5-triene **48** (Scheme 24).[37] Next, using the Negishi protocol, the bromide was cross-coupled in preference of the chloride. Then, in a separate step, the chloride **49** was subjected to Sonogashira coupling to obtain 3,5,7-trien-1-yne **50**. Further three steps of elaboration delivered the naturally occurring tetraenynone **51**, isolated from plants belonging to the Ombellifer family.[38]

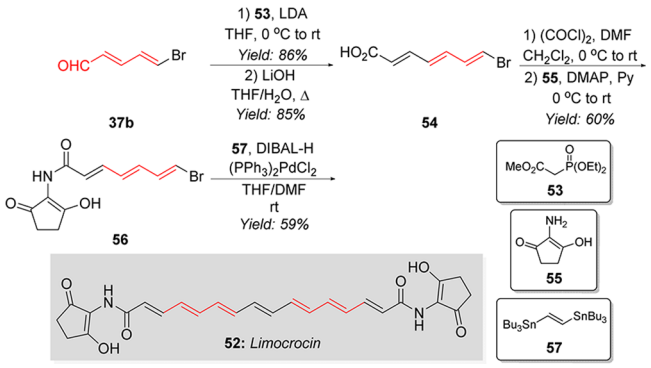
Some naturally occurring unsaturated amides have been prepared by Taylor and co-workers, tracing back the retrosynthetic origin to (2*E*,4*E*)-**37b**.[39] The polyene diamide

Scheme 24. An Orthogonal all-*E* 1,6-Dihalohexatriene



limocrocin **52** was isolated from *Streptomyces limosus* and behaves as a specific inhibitor of reverse transcriptase.[40] Prominently featuring an all-*E* heptaene moiety as the functional linker, the symmetry within the natural product opted for a stitching approach. Consequently, (2*E*,4*E*)-**37b** was elongated in a Horner−Wadsworth−Emmons homologation, subjected to saponification and amidation to yield the all-*E* trienoic amide **56** (Scheme 25). Finally, capitalizing on the Stille reaction, all-*E* trienoic amide **56** was cross-coupled with the tin-based stitching reagent **57** to afford limocrocin **52**.

Scheme 25. Synthesis of an All-*E* Polyene



In general, olefination protocols in combination with (2*E*,4*E*)-**37b** facilitate the rapid assembly of polyene scaffolds found in a number of natural products. The polyenyne butanolides, xerulin and dihydroxerulin, exhibiting potent inhibition of cholesterol biosynthesis, are further examples of molecules that have been prepared via this type of strategy.[41]

Direct 1,2-addition of a nucleophile to (2*E*,4*E*)-**37b** is a viable approach in total synthesis. The challenge is to enforce stereochemical control over the resulting secondary alcohol, lest the level of oxidation is adjusted. Osteopanic acid, a plant anticancer agent featuring a 2,4-diene-1,6-dione, was obtained by the latter strategy.[42] Particularly, aldol condensation across the aldehyde moiety of (2*E*,4*E*)-**37b** represents a powerful transformation in the context of pyridinium salts and their application. In the simplest execution, dehydration will just furnish a new double bond, i.e., a two-carbon homologue. However, the addition of a chiral enolate to (2*E*,4*E*)-**37b** can facilitate the asymmetric synthesis of secondary allylic alcohols present in a number of natural products.

An example of a stepwise dehydration protocol is provided by Kobayashi and co-workers in their synthetic efforts toward

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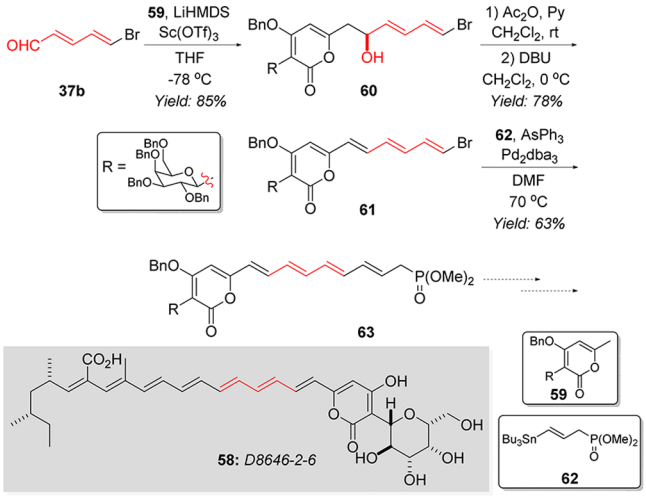
the telomerase inhibitor D8646-2-6 (**58**).[43] In an extended aldol reaction, the lithium anion of carbohydrate-containing pyrone **59** was added to (2*E*,4*E*)-**37b** (Scheme 26). In order to

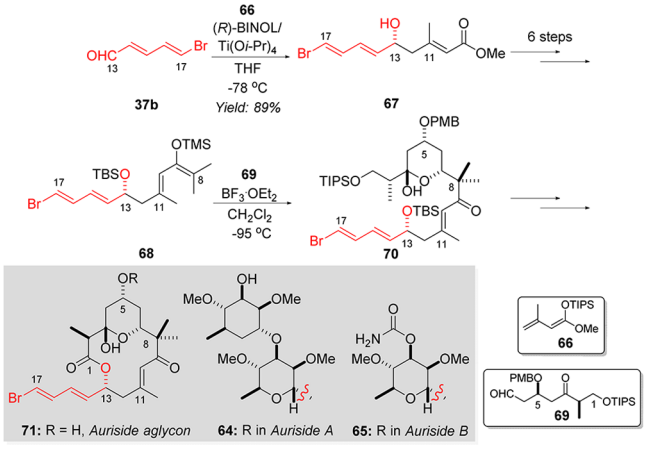
Scheme 26. Aldol Condensation Strategy



expedite adduct formation, the presence of a Lewis acid such as $Sn(OTf)_2$ or $Sc(OTf)_3$ was needed. To gain control of the olefin geometry, the adduct **60** was dehydrated in a following step by a one-pot acylation/elimination procedure, which gave the all-*E* bromotriene **61**. Stille coupling of the bromo terminus with vinylstannane **62** provided the advanced fragment **63** ready for a Horner−Wadsworth−Emmons reaction.

The marine polyketides (−)-auriside A (**64**) and (−)-auriside B (**65**) feature a unique structural motif having an *E*,*E* bromodiene appended to the macrolide core. Bisecting the structure in a northern and southern hemisphere, Paterson and co-workers traced back the prominent portion to (2*E*,4*E*)-**37b** (Scheme 27).[44] Identifying the southern hemisphere as the

Scheme 27. Asymmetric Mukaiyama Aldol Strategy



C8−C17 subunit **68**, the key synthetic transformation of its making, was an asymmetric vinylogous Mukaiyama aldol condensation between (2*E*,4*E*)-**37b** and silyl dienolate **66**, facilitated by the chiral Lewis acid derived from (*R*)-BINOL/$Ti(O\text{-}i\text{-}Pr)_4$. Having prepared the C1−C7 subunit **69** in parallel, the two hemispheres were joined in yet another Mukaiyama aldol reaction, relying on 1,3-*anti* induction from the C5-ether to set the C7-stereocenter of the tetrahydropyran-2*H*-ol ring, which is present in the acyclic backbone **70**. Elaboration, involving adjustment of oxidation level, macrolactonization and deprotection furnished the aglycon **71**. The total syntheses of (−)-auriside A (**64**) and (−)-auriside B (**65**) were accomplished in 18 steps (1.7% overall yield) and 17 steps (3.5% overall yield), respectively. An adaption of this strategy was applied by Paterson and co-workers in a total synthesis of the structurally related (+)-dolastatin 19.[45]

Olivio and Tello-Aburto have also approached the aureside aglycon **71**, conducting a formal synthesis based on a strategy which features the adduct between a chiral *N*-acetylthiazolidinethione and (2*E*,4*E*)-**37b**.[46] The applied protocol takes advantage of a process commonly referred to as the Nagao acetate aldol reaction and invokes a closed/chelated transition state as the origin of induction.[47]

Within recent years oxygenated polyunsaturated fatty acids (PUFAs) have attracted a significant amount of attention. The reason being, that a number of privileged structures originating from eicosapentaenoic acid, docosahexaenoic acid and n-3 docosapentaenoic acid, have been identified as specialized pro-resolving mediators, due to their ability to modulate acute inflammatory response at the receptor and on a cellular level.[48] In an approach toward the synthesis of members belonging to this class of compounds, Hansen and co-workers have developed a unified asymmetric strategy which takes advantage of the Nagao acetate aldol reaction on (2*E*,4*E*)-**37b** (Figure 2).[49] Illustrated by the total synthesis of protectin D1 (**72**), the

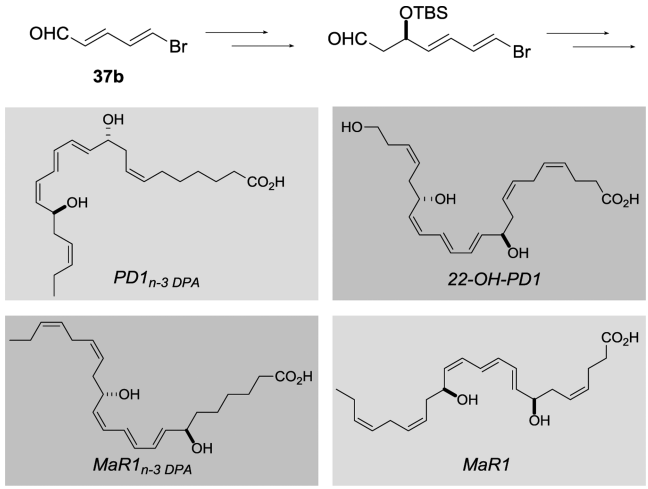


Figure 2. Oxygenated PUFAs via Nagao acetate aldol reaction.

sequence commenced with enantioselective formation of the key C8−C14 middle fragment **74**, obtained via asymmetric aldol reaction on (2*E*,4*E*)-**37b** (Scheme 28). Condensation with Wittig reagent **75** to install the C1−C7 portion in a highly *Z*-selective manner provided the advanced intermediate **76** carrying a bromide as functional handle. The final assembly of the carbon framework was executed by Sonogashira coupling with the C15−C22 fragment **77**. Further three steps delivered the target molecule **72** by a highly convergent route, encompassing eight steps (longest linear sequence) and an overall yield of 15%.

At the opposite end of the biological activity spectrum we find the leukotrienes, acting as pro-inflammatory agents.[50] Some oxygenated PUFAs belonging to the structural class of

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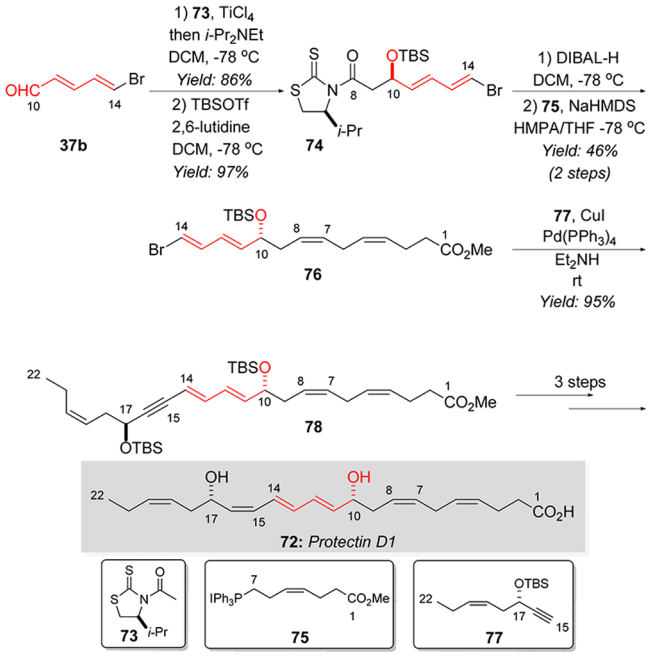
Scheme 28. Example of Asymmetric Nagao Acetate Aldol Reaction



leukotrienes have also been prepared via strategies utilizing (2*E*,4*E*)-**37b**.[51]

In conclusion, ring-opening of pyridinium salts provides an entry to polyene motifs that are ubiquitous in natural products. Thus, iteration of the orthogonal functional pattern has been featured in syntheses of macrolides, polyketides and oxygenated polyunsaturated fatty acids, to name but a few. On the other hand, the latent dienal moiety can also participate in cycloadditions and pericyclic rearrangements, enabling an entry into polycyclic natural products. In view of the examples provided herein, it is easy to envision the future implication of pyridinium salts as a dienal precursor in total synthesis.

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Notes

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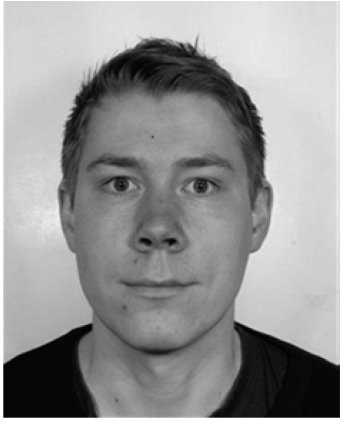

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