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Natural product synthesis facilitated by the deuterium isotope effects (DIE)

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ABSTRACT

When a deuterium atom (^{2}H or D) replaces a hydrogen atom (^{1}H) in a reactant molecule, the observed change in the rate (kinetic isotope effect, KIE) or equilibrium (equilibrium isotope effect, EIE) of a chemical reaction is known as a deuterium isotope effect (DIE). Because deuterium is twice as heavy as hydrogen, its zero-point energies (ZPEs), which are the lowest vibrational energies that a bond may have, differ significantly. Due to the obvious advantages of deuterium isotope effects (DIE) in total synthesis and mounting importance of deuterated drugs in pharmaceutical industry, development of synthetic routes to these deuterium-based active drugs *via* DIE is a challenging and important task. The primary goal of this mini-REVIEW is to demonstrate the novel uses of the DIE effect by placing the D atom at specific locations on drug molecules. This has been shown to serve as a "removable blocking group" to enhance yields and selectivity, while suppressing side reactions in the crucial stages of the complete synthesis of certain drug molecules. This review may be served as a perspective or guide for future study as well as inspire further innovative advancements in the field of total synthesis, and stimulate their applications in the related mechanistic studies.

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1. Introduction

Deuterium was discovered by Harold C. Urey in 1931, which led him to win Nobel Prize in Chemistry in 1934 [1]. Since deuterium has an abundance of 0.0115 % in nature, it is a stable isotope that can be handled in a laboratory setting without the need for specific handling authorizations or radiation safety precautions. Deuterated medicines have certain advantages over non-deuterated drugs when it concerns medicinal chemistry, including excellent tolerability, improved pharmacokinetics, and a boost in active metabolites in the body by reducing toxic by-product [2].

When a medication is metabolized by enzymes by a process that includes breaking a C–H bond at a rate-determining step (RDS), deuteration at that location can considerably slow down the reaction due to the fact that C–D bond is stronger than the C–H bond. Because of this, replacing H with D in pharmaceutical sciences usually results in a longer half-life that slows down certain metabolic reactions and permits less frequent dosing. Additionally, the deuterated drugs may improve therapeutic safety in advanced clinical approved trials. For instance, Deutetrabenazine (Austedo®) can be used to treat tardive dyskinesia and chorea associated with Huntington's disease. Donafenib is used to treat hepatocellular cancer. Clinical trials are being conducted on deuterated enzalutamide (prostate cancer) and deuterated linoleic acid (Friedreich's ataxia) (Fig. 1) [3–6]. Because deuterium can be identified by mass spectrometry with a high degree of sensitivity, this makes it an excellent tracer nuclide in organic chemistry. Till date, deuterium labeling applications have significantly increased as a result of this mindset, especially in the multi-step transformations in total synthesis [7,8].

Deuterium isotope effect (DIE), or also known as kinetic isotope effect, is observed in the different reaction rates between the isotopically labelled deuterated molecules and the non-deuterated compounds [9–12]. The lower kinetic acidity but higher activation energy of C–D bond relative to a C–H bond has been particularly

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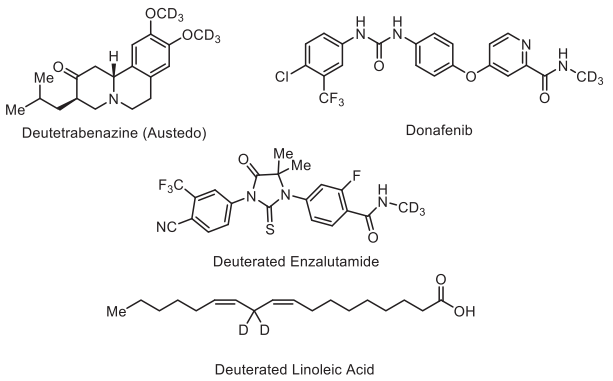


Fig. 1. Representative deuterated clinical approved pharmaceuticals.

useful in understanding the reaction mechanism, because it provides primary DIE evidence if a labelled bond is formed or broken when the rate-determining step is involved through kinetic isotope effect ($KIE = K_H/K_D$) [13,14]. A secondary hydrogen isotope effect arises in cases where the C–H or C–D bond remains intact during the rate-limiting step. In this regard, usually, modifications in hybridization or the use of hyperconjugation may result in the production of secondary KIEs [15].

There will be significant variations in the zero-point energy (ZPE) discrepancies between C–H and C–D bonds due to the difference in force constant for the out-of-plane bend of a sp^3 hybrid *versus* a sp^2 hybrid. The frequency of the in-plane bend also varies significantly between sp^2 and sp hybrids.

Deuteration is a technique that, despite the fact that there are many different ways to do it, is constantly evolving and is employed in many different sectors, including the biological sciences and drug industries. After the approval of deutetrabenazine as first deuterated drug by FDA [16]. The race to develop more efficient synthetic routes to deuterated drugs has resulted in enormous increase in the usage of deuterium isotope effect in chemical and biological synthesis.

The use of DIE during total synthesis has opened up new possibilities for the development of affordable and effective approaches to get naturally occurring compounds of biological and pharmacological importance [17–19]. NMR along with GC–MS or LC-MS measurements of a deuterium labeled species can be utilized to investigate electronic, steric, and related effects, due to the sensitive properties of DIEs toward substrates or transition-state of the intermediate species [20]. As a result, DIE has recently been used as an important tool in the total synthesis of valuable natural products, most occasionally with the aim to suppress side product formation in organometallic reactions [21–24], or to facilitate C–H bond functionalizations (Fig. 2) [25–30]. Due to the importance of DIE and the advantages of deuterated drugs in medicinal chemistry, substantial advancement has been made toward the development of quick and practical methods for the late-stage incorporation of deuterium in organic compounds. In a recent summary, Atzrodt and Marc Reid have summarized the advancements in the application of hydrogen isotopes in the life sciences [31]. The

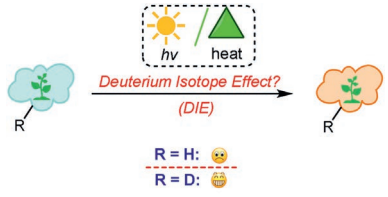


Fig. 2. The use of DIE in the total synthesis of natural products.

catalysts/immobilization strategies or visible light-induced deuteration enforced in the D-labelled organic compounds were also demonstrated [32,33]. However, the significant advances in synthetic chemistry for the complete synthesis of physiologically natural compounds by deuteration or with the aid of DIE, have not yet been fully explained.

In this mini review, we would like to showcase the rapidly expanding use of DIE in the total synthesis of natural products over the previous few years [34]. We hope that this review may be served as a perspective or guide for future study as well as spark further advancements in the field of applications of DIE in new natural product synthesis and the related mechanistic studies.

2. Applications of DIE in total synthesis of natural products

2.1. Fredericamycin A

The first demonstration of the utility of deuterium kinetic isotope effects in natural product synthesis is the laboratory synthesis of Fredericamycin A.

Fredericamycin A is a hexacyclic quinone-based natural antibiotic, which was isolated in 1981 from soil bacterium *Streptomyces griseus* at Frederick Maryland [35]. It was reported to possess potent antifungal, antibacterial activities and exhibits cytotoxic activities against CD8F mammary cell lines, Du-145 prostrate tumor, murine leukemia KB and P338D1 mouse leukemia [36]. Structurally, Fredericamycin A contains two sets of *peri*–hydroxy tricyclic aromatic moieties joined through a chiral spiroquaternary carbon center. Due to its significant bioactivities and unique molecular architecture, numerous synthetic studies have been reported for the total synthesis of Fredericamycin A [37,38].

Formation of the unusual spiroring system of Fredericamycin A is a challenging task. For this, Clive and co-workers developed an interesting intramolecular 6-*endo*-*trig* radical cyclization reaction of **1** (Fig. 3) [39]. Besides the desired product **3a** obtained in 48% yield, an unwanted byproduct **2a** resulting from intramolecular hydrogen transfer was also produced in comparable amount. The authors then tested deuterium kinetic isotope effects (KIE) to avoid this undesired atom transfer side reaction. Treatment of the deuterated substrate **1** under same conditions, the ratio of desired product **3b** to that of the byproduct **2b** was now improved to be 9.7:1 and the desired cyclization product **4** was obtained in ≥70% yield. Compound **4** was then conveniently transformed into the spiroquinone **5**, a key segment of Fredericamycin A.

2.2. Guanacastepene A

The Guanacastepene diterpenes were discovered by the groups of Clardy and Sterner, respectively (Fig. 4) [40]. They share a tricyclic neodolastane carbon skeleton with two angular methyl groups in an anti-1,4 relationship. In view of their attractive structures and promising biological activities [41,42], guanacastepenes have brought up various interesting synthetic methods and strategies, and continue to synthetic chemists [43–47].

Danishefsky and co-workers reported their synthetic studies for the synthesis of the highly functionalized tricyclic skeleton of Guanacastepene A [48–51]. For the left [5.3]-bicyclic system, they utilized a reductive cyclopeptanone annulation of **6** (Fig. 5). The reaction proceeded well and could provide gram quantities of the desired product **8a**. But a considerable amount of the uncyclized byproduct **7a** was also obtained. This is presumably due to protium transfer from the α-carbon to the vinyl lithium species. Therefore, the authors prepared deuterated compounds **6b** and **6c** in the hope of using DIE to suppress this protium transfer process. Pleasingly, the yield of the desired deuterated hydroazulene **8c** was greatly improved.

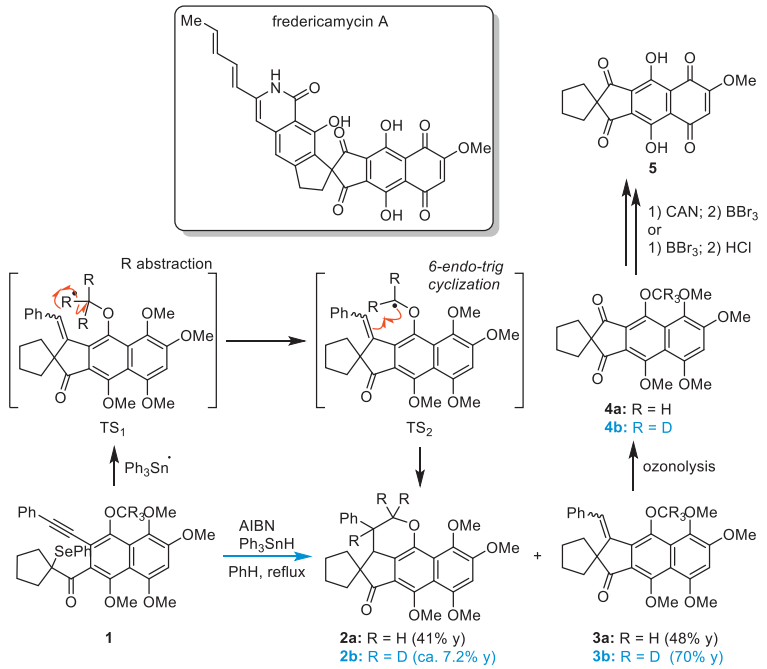


Fig. 3. Clive's studies of deuterium isotope effects for improving the key 6-*endo-trig* radical cyclization during the synthesis of Fredericamycin A. CAN = ceric ammonium nitrate.

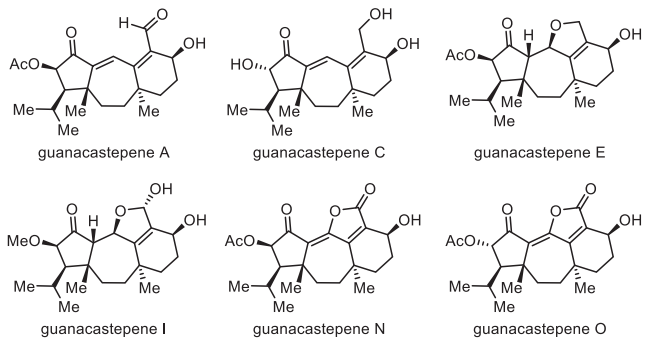


Fig. 4. Representative guanacastepene natural products.

2.3. Aziridinomitosenes

Aziridinomitosenes are a class of clinically used tetracyclic antibiotics, are structurally related to mitomycin C and possess comparable bioactivities [52]. FR66979 (**9**) and FR900482 (**10**) are also believed to generate the reduced aziridinomitosene intermediate (**11**) responsible for their activities [53]. Danishefsky [54] and Egbertson could detect the compound **11** *via* NMR analysis, but the molecule was too unstable to be isolated [55]. The quinone derivative is considerably more stable. In 1999, Jimenez and Dong reported total synthesis of aziridinomitosene **A** having a quinone structure [56]. Thus, the development of efficient method to access aziridinomitosenes with good stability as well as activity becomes an important and challenging task.

In 2002, Vedejs and Little reported total synthesis of aziridinomitosenes by a novel anionic cyclization strategy (Fig. 6) [57]. Subjecting compound **13**, easily prepared through a S_N2 reaction, they obtained the desired product albeit with low yields. Careful deuterioethanol quenching experiments allowed them to isolate compounds **18b** and **18c** as the major products. This revealed that the indole C–H lithiation dominated over the desired tin-lithium exchange and suppressed the desired intramolecular cyclization. To their delight, treatment of the deuterated compound **14** under same reaction conditions as for **13**, followed by trapping with PhSeCl for elimination, they could get **15** in 71 % yield. Deuterium served to block the undesired indole C–H lithiation and was smoothly removed during the elimination step. Further simple transformations then provided new aziridinomitosenes **16** and **17**.

2.4. Norzoanthamine

Marine natural products usually have interesting structures and possess unique their biological activities. They play an important role in modern drug discovery. Zoanthamine alkaloids are a group of structurally diverse marine natural products (Fig. 7), mainly

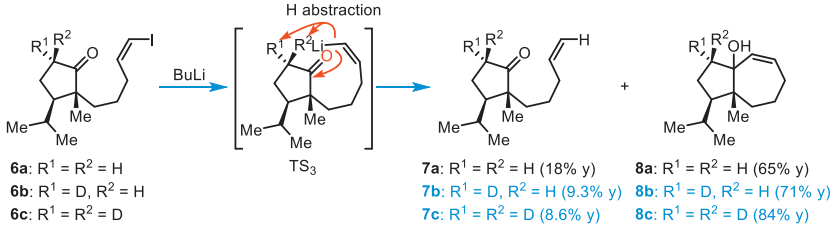


Fig. 5. Danishefsky's intramolecular cyclization of an alkenyllithium species onto a ketone for the synthesis of Guanacastepene A.

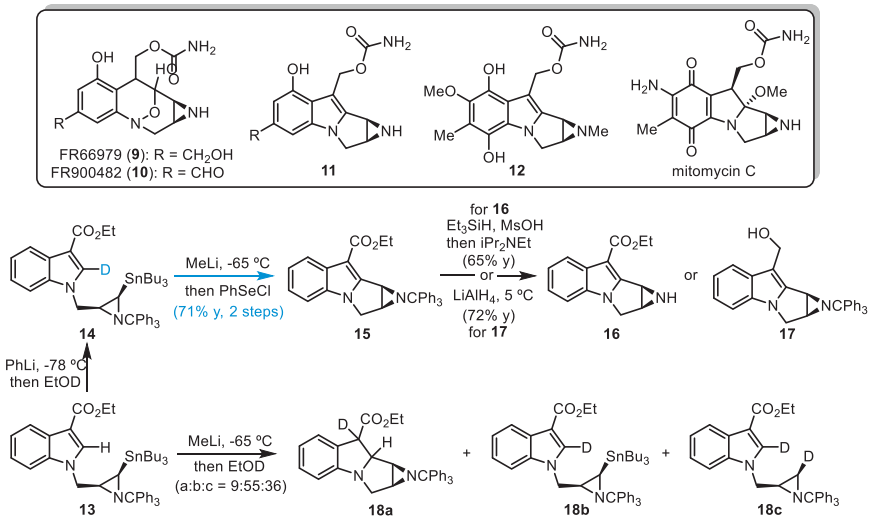


Fig. 6. Vedejs' total synthesis of aziridinomitosenes facilitated by deuterium as a removable blocking group.

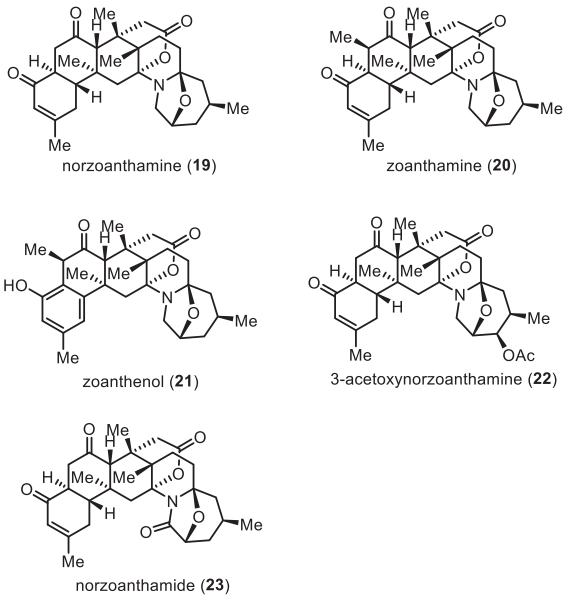


Fig. 7. Representative zoanthamine alkaloids.

found from colonial zoanthids of the genus Zoanthus [58]. Biological studies revealed that norzoanthamine (**19**) is capable of suppressing the loss of bone strength and mass caused by ovariectomy in mice [59,60]. This suggests that norzoanthamine might be applicable as an anti-osteoporotic drug. Due to its unique structural features and promising biological activities, norzoanthamine has attracted much attention from the synthetic community. To date, the groups Miyashita, Kobayashi and Gao had achieved its total synthesis [61].

Miyashita and co-workers devised their synthesis by means of an alkyne segment to join the other aldehyde segment (Fig. 8) [62]. In the final alkyne formation step by elimination (**24** to **25**), they found that a 1,5-HAT process happened to give undesired byproduct **26a** in 30 % yield, which greatly influenced the yield of the desired alkyne product **27a**. To solve this issue, they prepared the deuterated compound **24b** and subject to the same reaction conditions. Due to deuterium kinetic isotopic effects (KIE), the 1,5-HAT process was substantially slowed, and the yield of the desired alkyne **27b** was improved to be 81 %. The deuterium atoms could be easily removed in the later stage of oxidation to acid, and the first total synthesis of norzoanthamine (**19**) was finally completed in impressive overall yields by Miyashita and co-workers.

2.5. Oxidized welwitindolinones and (−)-N-methylwelwitindolinone C isonitrile

Welwitindolinone natural products possess unique [4.3.1]-bicyclic bridged ring systems with various stereogenic centers and functional groups [63]. Some of them showed promising activity against drug-resistant cancer cells. Since their isolation, welwitindolinones have inspired many synthetic chemists to devise numerous intriguing strategies for their syntheses [64]. In 2011, both the groups of Garg [65,66] and Rawal [67] reported the first total synthesis of oxidized welwitindolinones.

Based on their previous synthetic studies, Garg and co-workers strategically employed KIE to improve the efficiency of forging the C–N bond *via* the challenging nitrene insertion reaction (Fig. 9) [68]. As shown, with the deuterated compound **32b**, the yield of the desired product **34b** was significantly improved and the major byproduct ketone **33b**, presumably resulting from insertion of the nitrene species into the C–H bond at C-10, was suppressed from 25 % yield to 8 % yield. From **35**, (−)-*N*-methylwelwitindolinone C isothiocyanate (**36**), (−)-3–hydroxy *N*-methylwelwitindolinone C isothiocyanate (**37**), (−)-*N*-methylwelwitindolinone C isonitrile (**40**), and (−)-3–hydroxy *N*-methylwelwitindolinone C isonitrile (**39**) were then quickly accessed over several simple transformations.

2.6. Taxol

Taxol (**46**, paclitaxel), a well-known anticancer medicine used to treat breast, lung, ovarian, and Kaposi's sarcoma, is a natural diterpenoid first isolated from the bark of the Pacific yew tree (Taxus brevifolia) [69]. Structurally, Taxol features [6−8−6−4] carbon skeleton highly oxygenated and functionalized. Taxol represents one of the most formidable challenging synthetic targets, and has attracted significant interest from synthetic chemists, leading to the development of numerous interesting strategies and novel synthetic methods over decades [70].

The Baran group initiated their remarkable two-phase synthesis in 2007, and eventually reported their successful synthesis of

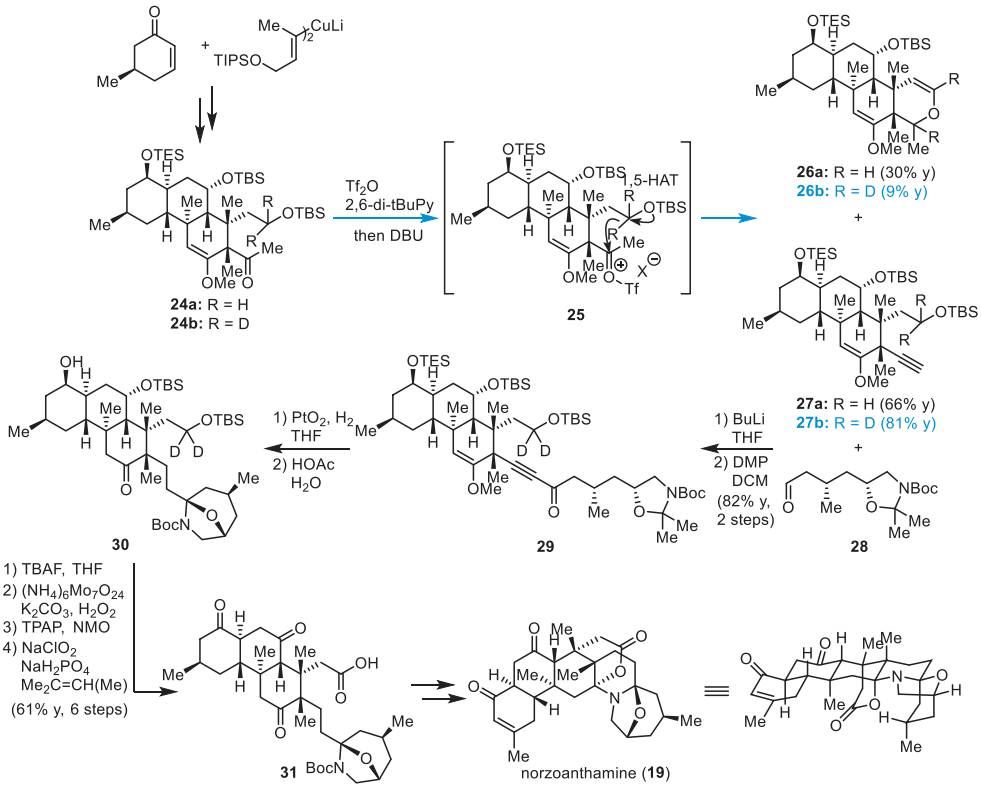


Fig. 8. Miyashita's use of kinetic isotopic effects in the total synthesis of norzoanthamine (**19**).

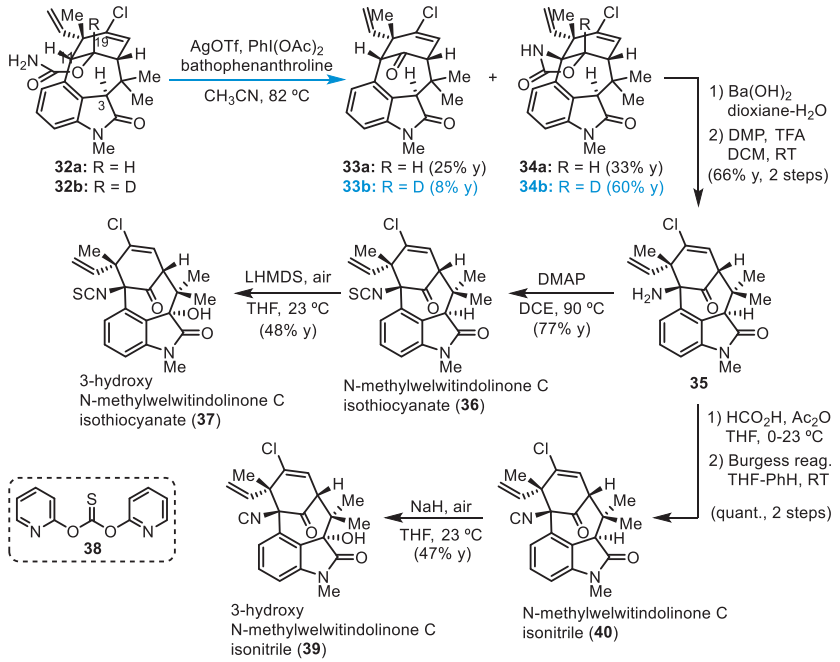


Fig. 9. Garg's strategic use of kinetic isotopic effect in the total synthesis of welwitindolinone natural products.

Taxol in 2020 (Fig. 10) [71]. At the stage of introducing the oxidation state at C-1 and $\Delta^{5,6}$-olefin simultaneously from **41a** by DMDO oxidation, they observed ketone **42a** resulting from oxidation of the secondary alcohol, was the major product instead of the desired one **44a**. Then, by means of C-2 deuterated substrate **41b**, this undesired alcohol oxidation process is pleasingly significantly retarded, due to a β-secondary KIE [72,73]. Furthermore, the intended product **44c** was achieved in a better yield of 49 % than 9 % (**44a**), while utilizing $CHCl_3$ as the solvent instead of acetone, which probably improves the reactivity of DMDO through H-bonding. Following oxidation by TPAP and NMO then produced ketone **45**, an important intermediate en route to Taxol.

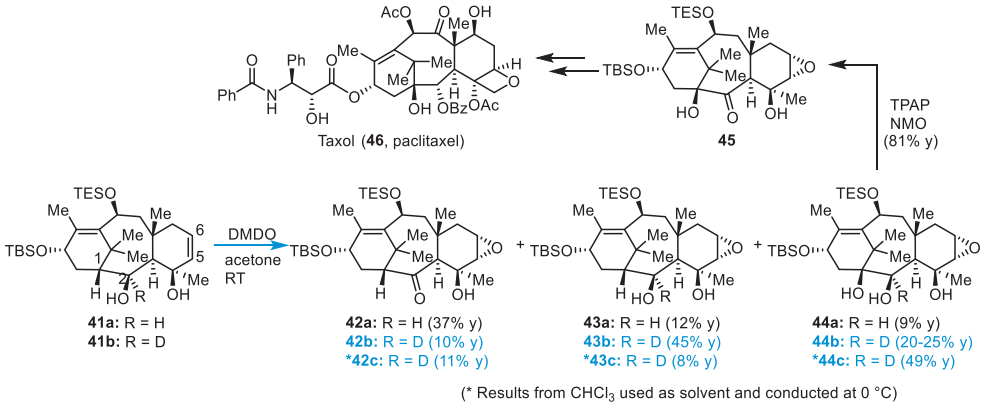


Fig. 10. Baran's application of deuterium isotope effects in the total synthesis of Taxol (**46**).

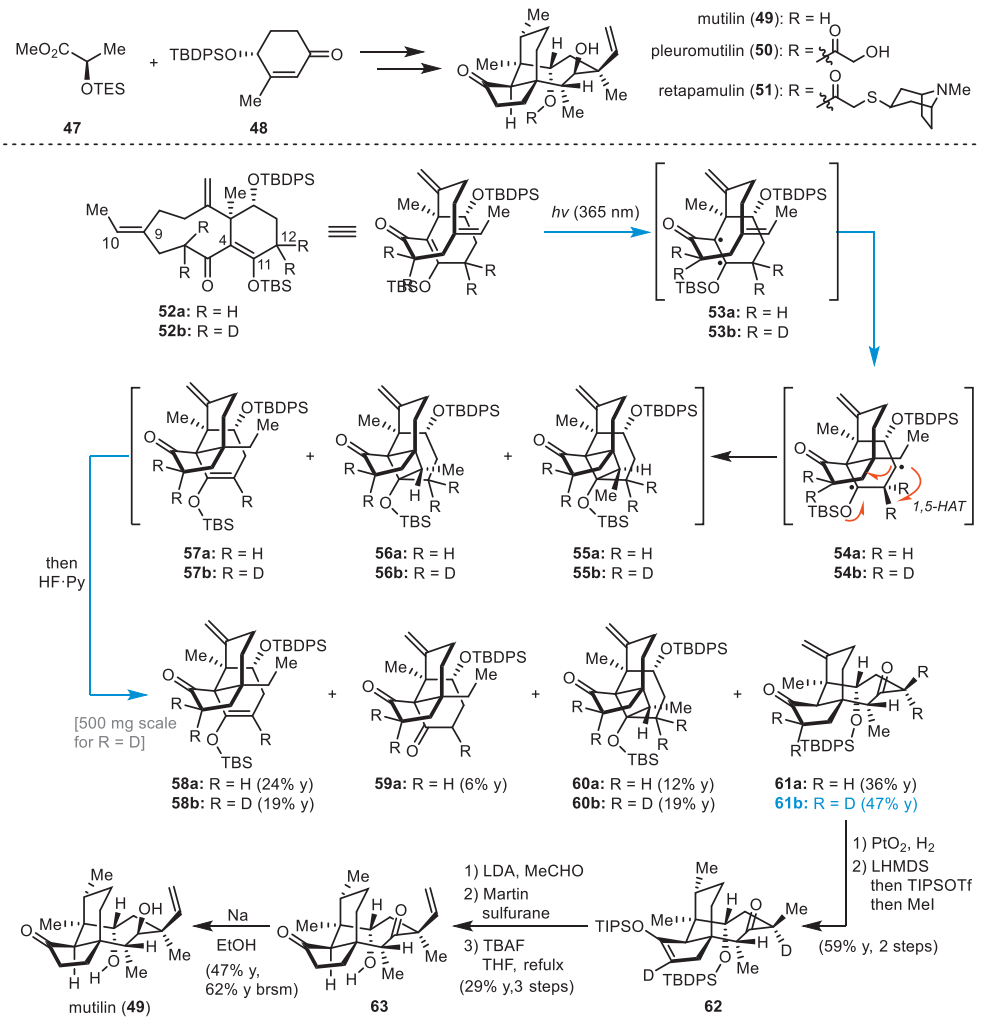


Fig. 11. Luo's total synthesis of (+)-mutilin (**49**) *via* a transannular [2+2] cycloaddition/retro-aldol fragmentation reaction.

2.7. (+)-Mutilin

Antibiotics can effectively prevent and treat bacterial infections. However, bacteria can adapt to the frequent use of them and finally become antibiotic-resistant. Antibiotic resistance [74], with new resistance mechanisms emerging and spreading as well, has thus become one of the biggest threats to global health [75]. The importance of discovering new antibiotics cannot be overstated. Among these efforts, the natural diterpene pleuromutilin (**50**) was found to be able to inhibit the growth of Gram-positive pathogens through binding to the peptidyl transferase center of the bacterial ribosome [76]. And the development of resistance is slow for this family. Due to promising antibacterial activities and its unique 5–6–8 densely functionalized tricycle, pleuromutilin had attracted

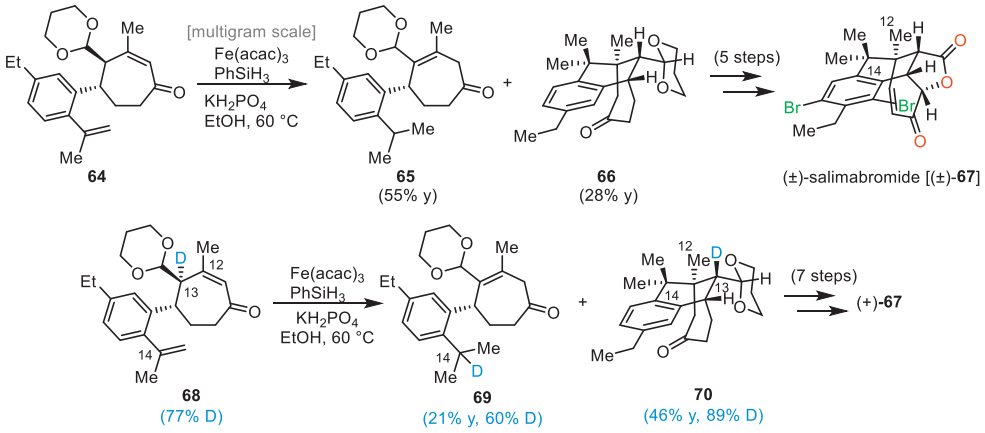


Fig. 12. The HAT-cyclizaiton for the total synthesis of salimabromide (**67**).

significant attention from the synthetic and medicinal community leading to seven elegant total syntheses [77] and the FDA-approved topical antibiotic retapamutilin (**51**), to date [78,79].

In 2022, Luo and co-workers reported their total synthesis of (+)-mutilin (**49**), interconvertible with its (+)-pleuromutilin (**50**), from simple (+)-lactate derivative (**47**) and chiral enone (**48**) (Fig. 11) [80]. To construct the key 5–6–8 tricyclic framework, they devised a novel tandem photo-induced transannular [2 + 2]-cycloaddition/retro-aldol fragmentation reaction of 6–9 bicyclic intermediate (**53a**). The authors could obtain the desired product **61a**, but also observed comparable yields of the intramolecular 1,5-HAT side products **58a** and **60a**, besides the stable [2 + 2]-cycloaddition diastereomeric adduct **59a**. To suppress the undesired 1,5-HAT pathway, they then turned attention to deuterium kinetic isotope effect [81]. Pleasingly, with the deuterated compound **52b** under same conditions, the yield for the desired product was improved and the yield for the 1,5-HAT side product was significantly suppressed. Subsequent few steps, including exchanging deuterium to hydrogen, then completed the total synthesis of (+)-mutilin (**49**).

2.8. Salimabromide

In 2013, König and coworkers discovered the polyketide salimabromide (**67**), the first secondary metabolite from the *Plesiocystis/Enhygromyxa* clade of marine myxobacteria [82]. It exhibited potent inhibitory activities of *Arthrobacter cristallopoietes* but has extremely low natural abundance (only 0.5 mg was obtained from 64 L of culture). Structurally, salimabromide possess a unique benzo-fused [4.3.1] carbon skeleton with four contiguous stereocenters, including two vicinal quaternary ones. These highly compact structural features make salimabromide an appealing synthetic challenge [83]. In 2018, Magauer and coworkers successfully completed its first racemic total synthesis [84]. Meanwhile, Menche and coworkers soon reported their asymmetric synthesis of salimabromide and found that the natural salimabromide is actually in almost racemic form [85]. Strategically, both research groups resorted to an *in situ* ketiminium-[2 + 2]-cycloaddition of a tetralin-tethered amide to build the central bridged [4.3.1]-carbon framework [86].

Recently, we developed an intramolecular radical cyclization of diene **64** *via* hydrogen atom transfer (HAT) to construct the benzo-fused [4.3.1] carbon skeleton **66**, and finally achieved a concise synthesis of salimabromide **67** (Fig. 12) [87]. Unfortunately, the undesired 1,5-HAT side product **65** always dominated over the desired cyclization product **66**. This is presumably due to the steric hindrance associated during the cyclization as well as the proximity of the initially generated radical to the hydrogen atom at the γ-position of the enone moiety. The deuterium kinetic isotope effect (KIE) was then studied for this cyclization. To our delight, the deuterated compound **68** (75% D) to subjected to the same conditions, the desired cyclization product **70** could be obtained as the major product (46% y). Based on these interesting results, a new short asymmetric total synthesis of (+)-salimabromide was completed.

3. Summary and outlook

The DIE has been demonstrated to be a highly effective method for the cost-effective and selective protection of highly active protons, preventing side reactions and delivering greater yields of the target molecules during total synthesis. DIE is thus the method of choice for protecting active protons due to the benign methods for adding and removing D atom as a "removable blocking group". In this aspect, the typical applications of DIE by using the installation of D at specified places of clinically important drug molecules, such as Fredericamycin A, Guanacastepene A, Aziridinomitosenes, Norzoanthamine, oxidized Welwitindolinones and (−)-*N*-Methylwelwitindolinone C Isonitrile, Taxol, (+)-Mutilin, and Salimabromide, are summarized herein.

The trend of usage of DIE during total synthesis has seen a sharp increase during the past few years and is expected to continue as this approach. Owing to the importance and usefulness of DIE in organic synthesis, it is expected that more efficient, cost-effective and selective synthetic routes for the total synthesis of valuable natural products would be developed in the future with the help of DIE. It is necessary to develop more commercialized deuterated reagents, new catalytic systems and, optimized synthetic processes with the help of DIE, to efficiently synthesize deuterated drugs.

Moreover, since deuteration is an effective "isotope engineering" method, its principal utility is not only in discovering novel synthetic activities, but also in improving the pharmacokinetic and physicochemical features of molecules. As synthetic methods advance, their function will broaden beyond developing life-saving pharmaceuticals to enabling more stable materials, precise analytical methods, and efficient agricultural goods, making it a critical technology for molecular innovation in a variety of technologies.

In general, there is still plentiful of room for more efficient and goal orientated research in other areas of science with the help of DIE, and this review might help fellow scientists for future endeavors in this regard.

CRediT authorship contribution statement

Xiaojuan Chen: Writing – original draft, Investigation. **Yao Zhu:** Writing – original draft, Investigation. **Muhammad Suleman:** Writing – original draft, Investigation. **Ranjit Murmu:** Investigation. **Hai-Hua Lu:** Writing – review & editing, Project administration, Investigation. **Zhiyuan Chen:** Writing – review & editing, Supervision, Project administration, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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