Chemical Methods for the Synthesis and Modification of Neoclerodane Diterpenes

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Abstract

Diterpenes are a structural class of molecules that are derived from four isoprene subunits and are widespread throughout nature. A number of neoclerodane diterpenes have been found to have biological activity but a limited number of chemical investigations have been conducted. Recently, the neoclerodane diterpene, salvinorin A ($\mathbf{12}$) has been investigated due to its unique pharmacological profile. This review will discuss the chemical methods used to chemically modify and synthesize $\mathbf{12}$.

Keywords
diterpene; neoclerodane; salvinorin A; \textit{Salvia divinorum}

Terpenes are a wide variety of 10-carbon skeletons formed from the coupling of two isoprene subunits.\textsuperscript{1} They are ubiquitous in nature as they are used as biosynthetic building blocks in many living organisms including plants and animals.\textsuperscript{1} There are many different types of terpenes and they are classified by their structure.\textsuperscript{1} Diterpenes are one class that possess a core 20-carbon skeleton and are found in many different plant families and some animals.\textsuperscript{1} They are biosynthesized by two different pathways, the mevalonic acid pathway (MVA) or the deoxyxylulose phosphate pathway (DOXP).\textsuperscript{2–5} Diterpenes are of interest as many have been found to have biological activity. Some biologically active diterpenes include taxol (1), cafestol (2) and kahweol (3) (Figure 1). Diterpenes 1–3, isolated from \textit{Taxus brevifolia}\textsuperscript{6} and \textit{Coffea arabica} respectively,\textsuperscript{7,8} all display anticancer properties.

One type of structural class of diterpenes are clerodanes which are found in many different plant families and contain four contiguous stereocenters contained in a \textit{cis} or \textit{trans} decalin (4).\textsuperscript{9,10} Various clerodane diterpenes have been isolated and displayed biological activity. These include columbin (5), isolated from the roots of \textit{Calumbae radix}\textsuperscript{11} which has cancer chemo-preventive properties\textsuperscript{12} and clerocidin (6), isolated from \textit{Oidiodendron truncatum}\textsuperscript{13} which has shown antibiotic activity.\textsuperscript{13} Terpentecin (7), a microbial clerodane diterpene from
Neoclerodanes are a subtype of clerodane diterpenes that share the same absolute stereochemistry of clerodin (8). Neoclerodane 8 displays antifeedant properties and inhibits insect growth. These attributes have also been seen in other neoclerodanes such as ajugatansin A1 (9), and tafricanin A (10). These discoveries have implications for agriculture, as neoclerodane diterpenes, may have potential use as environmentally benign pest deterrents. One such example is callicarpenal (11), which has been shown to be a mosquito bite deterrent and a repellant of the blacklegged tick, *Ixodes scapularis* and the lone star tick, *Amblyomma americanum*.²⁸

Despite their biological properties, few synthetic works have been published on neoclerodane diterpenes.⁹,²⁰–²² One neoclerodane diterpene that has been investigated recently is salvinorin A (12). Neoclerodane 12 is isolated from the leaves of *Salvia divinorum*, and has shown to have hallucinogenic effects.²³–²⁶ However, 12 is unlike classical hallucinogens, as it does not interact with the 5-HT₂A receptor.²⁵,²⁷ Rather, 12 is a selective κ opioid agonist.²⁸ This was the first report of a neoclerodane diterpene to be active at opioid receptors, thus establishing neoclerodane diterpenes as a novel scaffold for opioid ligands.²⁷,²⁹ The chemical modification of 12 has been undertaken by several groups, including our own, to explore its chemical reactivity and to develop analogues that explore its pharmacophore at opioid receptors.³⁰–³⁵

Neoclerodane 12 is a highly functionalized molecule with a tricyclic core structure and seven chiral centers. Feeding experiments with [¹³C;3,4-²H₂]-1-deoxy-D-xylulose (DOX) have shown that 12 is biosynthesized in a manner consistent with the deoxyxylulose phosphate pathway.³⁶ The chiral center at the C8 position of 12 has shown to readily undergo epimerization under acidic or basic conditions (Figure 2).³⁰–³²,³⁴,³⁵ Epimerization at this center has shown to have great impact on biological activity.²⁶,³⁴,³⁷–³⁹ Despite these issues, several methods to explore the chemical reactivity of 12 have been developed.

Some of the initial chemical investigations of 12 attempted to remove the C2 acetate. Heating of 12 with strong base leads to the formation of 13 in 69% yield.⁴⁰,⁴¹ Treatment of 12 with KOH in CH₃OH leads to the oxidized products 14a and 15 in 53% and 37% yield respectively.³⁵ Using Ba(OH)₂ in place of KOH in CH₃OH gave 14b in 75% yield.³⁴ This transformation was also attempted using KCN in refluxing CH₃OH/tetrahydrofuran.⁴² While this method was able to remove the acetate, it led to epimerization at C8 as the major product with 51% yield. Selective removal of the C2 acetate of 12 was accomplished in 77% yield using Na₂CO₃ in CH₃OH,³⁰ yielding salvinorin B (16) (Figure 3). Ammonolysis of 12 using NH₃ and CH₃OH at 0 °C gave 16 in 15% yield with its C8 epimer in a 1:1 ratio.³²

Several groups have explored the reactivity of the carbonyl at C1 on the A ring of 12.³³,³⁴,⁴³,⁴⁴ The reaction of 12 with NaBH₄ at 35 °C gives the corresponding C1 alcohol as a 1:1 mixture of the α and β isomers in 40% yield.³³ However, this method also causes epimerization at C8 in 40% yield.³³ More recently, the reduction at C1 was improved by using an aqueous solution of NaBH₄ in tetrahydrofuran.⁴⁴ This method gave primarily the α-alcohol 17 in 77% yield with no epimerization at C8 and minimal reduction at C17.⁴⁴

Conditions to selectively hydrolyze the C4 carbomethoxy group have also been identified.³³,³⁴ Heating 12 with LiSEt in DMPOU followed by treatment with Ac₂O gave acid 18 and its C8 epimer in a 1.4:1 ratio with 73% overall yield.³⁷ Alternatively, heating 12 with Lil in pyridine also hydrolyzed the C4 ester to the acid in a reported 70% yield and avoided C2 deacetylation.³⁴ However, this method also caused C8 epimerization in a 1:1 ratio with 18.³⁴
Treatment of 12 with excess DIBAL-H in THF at −78 °C reduced the C17 lactone to give lactol 19 as a 1:1 mixture of epimers in 65% yield.37,42 The reduction appears quite selective as other functional groups are not effected and epimerization did not occur. However, 19 is not stable and undergoes elimination overnight.37

The reaction of 12 with NaIO4 and a catalytic amount of RuCl3•H2O in a mixture of acetonitrile/H2O/CCl4 affords acid 20 in 93% yield.45 Hydrogenation of 12 using rhodium on carbon gave 21 as a mixture of C13 epimers along with 2246 in 59% and 28% yield respectively. If palladium on carbon is used for the hydrogenation, hydrogenolysis (22) is favored.36,43 Bromination of the furan at the 2-position 23a, can be achieved using N-bromosuccinimide (NBS) in acetonitrile46 or CHCl3 40 with yields ranging from 10 – 60%.40,46 Dibromination at the 2- and 5 positions of the furan ring 23b, can be achieved using Br2 and CH2Cl2 at −30 °C in 52% yield.47 Treatment of 12 with Br2 and CH3OH affords dimethoxy, dihydrofuran 24 as a mixture of isomers in 61% yield.46 Finally, photo-oxidation of 12 gave the γ-hydroxy butenolides 25 as a 1:3 mixture of isomers in 25% yield.46

While 12 is a structurally complex natural product, a variety of reactions have been identified that have helped establish the chemical reactivity of 12, as well as prepare a wide array of analogues of 12 to explore its structure-activity relationships.48 Along with the work conducted to explore the chemical reactivity of 12, several groups have made attempts at the total synthesis of 12.49–53 To date, there have been two successful syntheses of 12.51,52 These efforts provide avenues to analogues that are difficult or unattainable by semi-synthesis.

In 2007, Evans and co-workers completed the first total synthesis of 12 in 33 steps with 4.5% overall yield.51 Evans envisioned 12 as being derived from macrolactone 26 through a transannular Michael reaction (Figure 4).54–56 Macrolactone 26 would then be assembled through the coupling of vinyl iodide 27 and aldehyde 28. Ketone 29 (Scheme 1) is prepared in 70% yield from the addition of propyne to 3-furaldehyde followed by oxidation with MnO2. Reduction of 30 with (R)-β-Methyl-oxazaborolidene gave alcohol 30 in 85% yield. Alkyne isomerization, using KH and H2N(CH2)3NH2, followed by carboalumination and protection of the alcohol with TES-Cl gave 27 in 68% yield. Claisen condensation57 of ethyl hydrogen malonate and thiazolidinethione 31 gave the β-ketoester 32 in 85% yield. Selective formation of the (Z) enol phosphate using lithium hexamethyldisilazide and CIPO(OEt)2 followed by Fecatalyzed cross-coupling gave olefin 33 in 92% yield. Aldol addition, alcohol protection and acetylde addition yielded propargylic alcohol 34 in 83% yield. Alcohol 34 was then subjected to protection, semi-hydrogenation, dihydroxylation and finally oxidative cleavage to give aldehyde 28 in 92% yield. The reaction of a grignard reagent derived from vinyl iodide 27 and aldehyde 28 gave alcohol 35 in 75% yield. Silation of 35 with TBSOTf, followed by TES deprotection using PPTS and hydrolysis using LiOH gave 36 in 93% yield. The Shiina procedure for macrolactonization followed by desilylation and oxidation gave 26 in 95% yield.58 Treatment of 26 with TBAF at −78 °C and warming to 5 °C triggered the transannular cascade to give the tricyclic compound 37 as a single diastereomer in 95% yield. Enol 37 was deoxygenated to 38 using a sequence of trflate formation, catalytic reduction and conjugate reduction. Deprotection of 38, followed by oxidation and esterification afforded 8-epi-16 in 95% yield. Finally, epimerization of the C8 position with K2CO3 in CH3OH, followed by acylation gave 12 in 78% yield.

In 2008, Hagiwara and co-workers also published a total synthesis of 12 in 20 steps with 0.15% yield.52 They envisioned 12 being synthesized from the hydroxy- ketone 39 through a linear series of functionalizations (Figure 5). Protection of the (R)-(-)-Wieland-Miescher ketone59 followed by treatment with NH4Cl in KOH and CH3OH gave the hydroxy-ketone 39 in 73% yield (Scheme 2). A reductive alkylation of 39 gave a mixture of 40 and 41 in 21% and 51% yield, respectively. Compound 41 was then deprotected and the resulting diketone was
subjected to double Wittig methylenation with NaHMDS and Ph$_3$PCH$_2$Br to give ester 42 which was immediately reduced with LAH and the corresponding diols protected to afford 43 in 54% yield. Hydroboration followed by oxidation gave di-aldehyde 44 in 94% yield. Protection of the formyl groups, deprotection of the TBS ether and subsequent oxidation gave aldehyde 45 in 78% yield. The reaction of 3-lithiofuran with 45 gave the desired 12S furfurylalcohol 46 and its 12R epimer in 66% yield and in a 2:3 ratio. Deprotection of the S isomer of 46, followed by oxidation and esterification gave 2-desacetoxy salvinorin A 47 in 90% yield. Treatment of 47 with NaHMDS and TES-Cl in THF at −78° gave the corresponding silyl enol ether which was then subjected to Rubottom oxidation to yield 2-epi-17$^{61}$ in 70% yield. Inversion of the stereochemistry at C2 using Mitsunobu conditions followed by acylation, gave 12 in 86% yield.

Diterpenes are a diverse class of natural products with several subtypes, including neoclerodanes. Neoclerodane 12 serves as a useful example for the development of methodology to modify other neoclerodane diterpenes. Modifications to the structure of 12 have aided in determining its chemical reactivity as well as provide a platform for analogue development. Attempts to remove the C2 acetate of 12 with base leads to a mixture of products. This reaction was later optimized using Na$_2$CO$_3$ and CH$_3$OH. The C1 carbonyl of 12 can be selectively reduced and the C4 methyl ester has been converted to the corresponding acid. The C17 lactone may be selectively reduced using DIBAL-H. The furan ring of 12 may be reduced or oxidatively degraded to the C13 carboxylic acid. The total synthesis of 12 has been accomplished by two different groups and offers a strategy towards obtaining analogues of 12 that are otherwise inaccessible by semi-synthesis. Further advances in the synthesis of neoclerodane diterpenes are likely to further develop this structural class of terpenes into useful biological probes.

Acknowledgments

The authors would like to thank the National Institute of Health and the National Institute on Drug Abuse, as well as the Universities of Iowa and Kansas for financial support of our ongoing research efforts. AL is currently supported by NIDA grant DA018151S1.

References and Notes

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Figure 1.
Structures of taxol (1), cafestol (2), kahweol (3), diterpene skeleton (4), columbin (5), clerocidin (6), terpentecin (7), neoclerodanes clerodin (8), ajugatansin A1 (9), tafricanin A1 (10), callicarpenal (11) and salvinorin A (12).
Figure 2.
Compounds obtained through basic hydrolysis of 12.
Figure 3.
Structures of selected modifications to 12.
Figure 4.
Retrosynthesis of 12 as proposed by Scheerer et al.\textsuperscript{50}
Figure 5.
Retrosynthesis of 12 as proposed by Nozawa et al.\textsuperscript{51}
Scheme 1. Synthesis of 12 by Scheerer et al.\textsuperscript{50} Reagents and conditions: (a) propyne, n-BuLi, Et\textsubscript{2}O, −78 °C; (b) (R)-\[\beta\]-Methyl-CBS catalyst, BH\textsubscript{3}•Me\textsubscript{2}S, −30 °C; (c): (1) KH, H\textsubscript{2}N(CH\textsubscript{2})\textsubscript{3}NH\textsubscript{2}; (2) Me\textsubscript{3}Al, Cp-\textsubscript{2}ZrCl\textsubscript{2}, I\textsubscript{2}, −45 °C; (3) TESCl, imidazole; (d) Ni-(R)-BINAP(OTf)\textsubscript{2}, 2,6-lutidine, BF\textsubscript{3}•OEt\textsubscript{2}, HC(OEt)\textsubscript{3}; (e) HO\textsubscript{2}CCH\textsubscript{2}CO\textsubscript{2}Et, i-PrMgCl, 65 °C; (f) LiHMDS; CIPO (OEt)\textsubscript{2}; (g) Fe(acac)\textsubscript{3}, MeMgCl, −20 °C; (h): (1) DIBAL-H, −78 °C; (2) MnO\textsubscript{2}; (3) Sn(OTf)\textsubscript{2}, N-ethylpiperidine, chiral auxiliary, −78 °C; (i): (1) TBSOTf, 2,6-lutidine; (2) K\textsubscript{2}CO\textsubscript{3}, CH\textsubscript{3}OH; (3) OsO\textsubscript{4}, NMO, NaI\textsubscript{2}; (4) Zn(OTf)\textsubscript{2}, (−)-N-Methyl-ephedrine, Et\textsubscript{3}N, 4-phenyl-1-butyn; (j): (1) BOMCI, NaHMDS, −78 °C; (2) Lindlar catalyst, H\textsubscript{2}; (3) K\textsubscript{2}OsO\textsubscript{4}, NMO, citric acid, 50 °C, Pb(OAc)\textsubscript{4}, K\textsubscript{2}CO\textsubscript{3}; (k) 27, n-BuLi, MgBr•OEt\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, −78 to 0 °C.
C; (l): (1) TBSOTf, 2,6-lutidine; (2) PPTS, CH₂OH; (3) LiOH, i-PrOH, H₂O; (m): (1) MNBA, DMAP, [0.0015 M]; (2) TBAF; (3) Dess-Martin periodinane; (n) TBAF, −78 to 5 °C; (o): (1) NaH, Comins reagent; (2) Pd(OAc)₂, dpf, Et₃SiH; (3) L-selectride, i-BuOH, −78 to −55 °C; (p) LiBF₄, acetonitrile/H₂O; (q) NaClO₂, TMSCHN₂; (r) K₂CO₃, CH₃OH; (s) Ac₂O, pyridine, DMAP.
Scheme 2.
Synthesis of 12 by Nozawa et al. Reagents and conditions: (a) (CH₂)₂(OTMS)₂, Me₃SiOTf, 15 Kbar, 40 °C; (b) KOH, CH₃OH/H₂O, 65 °C; (c) Li/NH₃, THF, −78 °C, alkyl iodide; (d) 3M HCl aqueous EtOH; (e) NaHMDS, Ph₃PCH₃Br, THF; (f) LAH, Et₂O, 0 °C; (g) TBSCI, DMAP, Et₃N, CH₂Cl₂; (h) NaH, MPMCl, DMF; (i) BH₃, tetrahydrofuran, 3M NaOH, H₂O₂; (j) PDC, AcONa, MS-4Å, CH₂Cl₂; (k) NaOMe, CH₃OH; (l) ethylene glycol, PTSA, 40 °C; (m) TBAF, THF; (n) PDC, AcONa, MS-4Å, CH₂Cl₂; (o) 3-Bromofuran, t-BuLi, THF, −78 °C; (p) PTSA, aceton, H₂O, reflux; (q) DDQ, H₂O, CH₂Cl₂, 0 °C; (r) PDC, 2-methyl-2-butene, DMA; (s) DCC, DMAP, CH₃OH, CH₂Cl₂; (t) NaHMDS, TESCl, THF; (u) m-CPBA, NaHCO₃, toluene, H₂O, 0 °C, AcOH; (v) PPh₃, DIAD, AcOH, CH₂Cl₂.