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Chemical methods for the synthesis and modification of neoclerodane diterpenes

Anthony Lozama [a,b], Thomas E. Prisinzano [b,*]

[a] Division of Medicinal & Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52240, USA
[b] Department of Medicinal Chemistry, College of Pharmacy, The University of Kansas, Lawrence, KS 66046, USA

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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 (**12**) has been investigated due to its unique pharmacological profile. This review will discuss the chemical methods used to chemically modify and synthesize **12**.

Terpenes are a wide variety of 10-carbon skeletons formed from the coupling of two isoprene subunits.[1] They are ubiquitous in nature as they are used as biosynthetic building blocks in many living organisms including plants and animals.[1] There are many different types of terpenes and they are classified by their structure.[1] Diterpenes are one class that possess a core 20-carbon skeleton and are found in many different plant families and some animals.[1] They are biosynthesized by two different pathways, the mevalonic acid pathway (MVA) or the deoxyxylulose phosphate pathway (DOXP).[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**) (Fig. 1). Diterpenes **1**–**3**, isolated from *Taxus brevifolia*[6] and *Coffea arabica*, respectively,[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 cis or trans decalin (**4**).[9,10] Various clerodane diterpenes have been isolated and displayed biological activity. These include columbin (**5**), isolated from the roots of *Calumbae radix*,[11] which has cancer chemo-preventive properties[12] and clerocidin (**6**), isolated from *Oidiodendron truncatum*,[13] which has shown antibiotic activity.[13] Terpentecin (**7**), a microbial clerodane diterpene from *Streptomyces* sp., has shown to be an antitumor antibiotic that targets DNA topoisomerase II.[14]

Neoclerodanes are a subtype of clerodane diterpenes that share the same absolute stereochemistry of clerodin (**8**).[2] Neoclerodane **8**, displays antifeedant properties and inhibits insect growth.[15] 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.[16] One such example is callicarpenal (**11**), which has been shown to be a mosquito bite detterant[17,18] and a repellant of the blacklegged tick, *Ixodes scapularis* and the lone star tick, *Amblyomma americanum*.[19]

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-HT_{2A} 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,[28] 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 center. Feeding experiments with [1-^{13}C;3,4-$^{2}H_2$]-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 (Fig. 2).[30–32,34,35] Epimerization at this center has shown to have great impact on biological activity.[26,34,37–39] Despite

* Corresponding author. Tel.: +1 785 864 4495; fax: +1 785 864 5326.
E-mail address: prisinza@ku.edu (T.E. Prisinzano).

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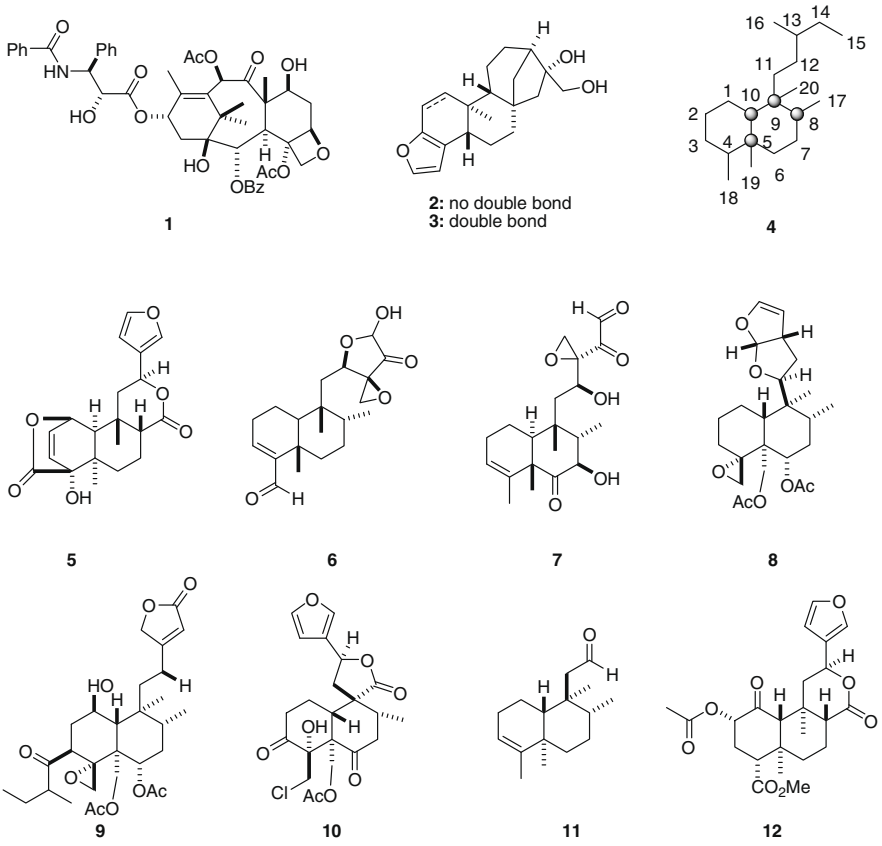


Figure 1. Structures of taxol (**1**), cafestol (**2**), kahweol (**3**), diterpene skeleton (**4**), columbin (**5**), clerocidin (**6**), terpentecin (**7**), neoclerodanes clerodin (**8**), ajugatansin A1 (**9**), traficanin A (**10**), callicarpenal (**11**) and salvinorin A (**12**).

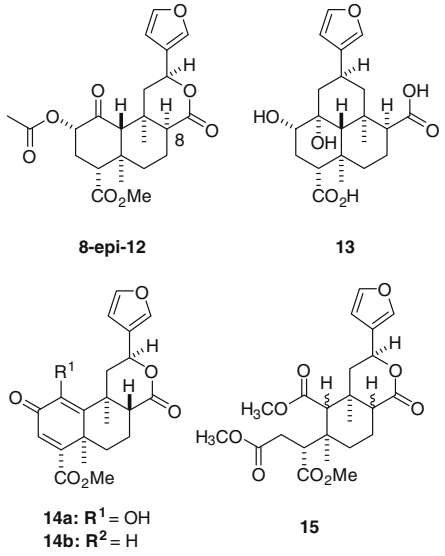


Figure 2. Compounds obtained through basic hydrolysis of **12**.

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 CH_3OH leads to the oxidized products **14a** and **15** in 53% and 37% yield, respectively.[35] Using $Ba(OH)_2$ in place of KOH in CH_3OH gave **14b** in 75% yield.[34] This transformation was also attempted using KCN in refluxing CH_3OH/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 Na_2CO_3 in CH_3OH,[30] yielding salvinorin B (**16**) (Fig. 3). Ammonolyis of **12** using NH_3 and CH_3OH 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**.[43,44] The reaction of **12** with $NaBH_4$ at 35 °C gives the corresponding C1 alcohol as a 1:1 mixture of the α and β isomers in 40% yield.[43] However, this method also causes epimerization at C8 in 40% yield.[43] More recently, the reduction at C1 was improved by using an aqueous solution of $NaBH_4$ 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 DMPU followed by treatment with Ac_2O gave acid **18** and its C8 epimer in a 1.4:1 ratio with 73% overall yield.[37] Alternatively, heating **12** with LiI 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 $NaIO_4$ and a catalytic amount of $RuCl_3{\cdot}H_2O$ in a mixture of acetonitrile/H_2O/CCl_4 affords acid **20** in 93% yield.[45] Hydrogenation of **12** using rhodium on carbon gave **21**

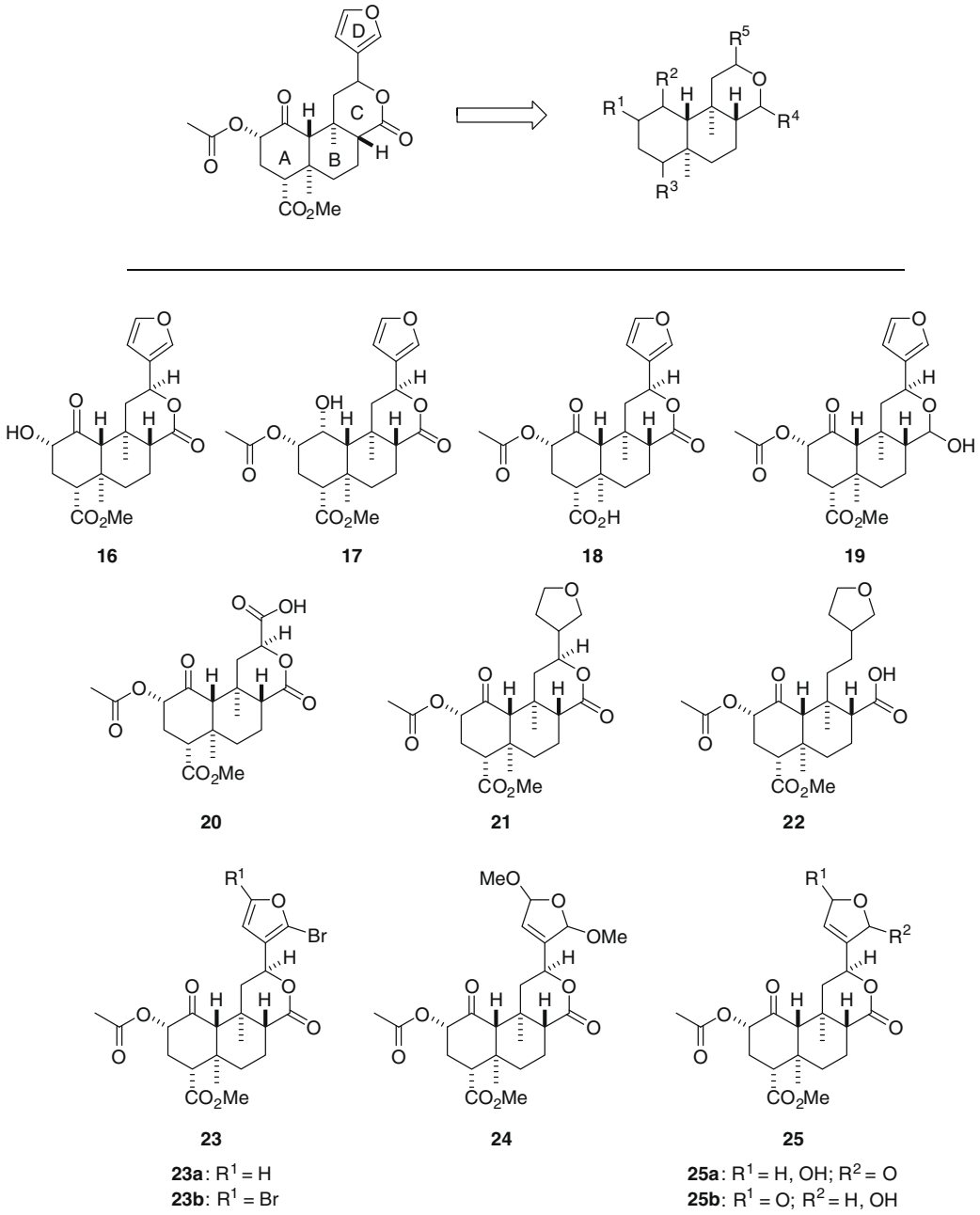


Figure 3. Structures of selected modifications to **12**.

as a mixture of C13 epimers along with **22**[46] 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*-bromosuccinamide (NBS) in acetonitrile[46] or $CHCl_3$[40] with yields ranging from 10% to 60%.[40,46] Dibromination at the 2- and 5-positions of the furan ring **23b**, can be achieved using Br_2 and CH_2Cl_2 at −30 °C in 52% yield.[47] Treatment of **12** with Br_2 and CH_3OH 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 (Fig. 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 MnO_2. Reduction of **30** with (*R*)-β-Methyl-oxazaborolidene gave alcohol **30** in 85% yield. Alkyne isomerization, using KH and $H_2N(CH_2)_3NH_2$, followed by carboalumination and protection of the alcohol with TES-Cl gave **27** in 68% yield. Claisen condensation[57] of ethyl hydrogen malonate and thiazolidinethione **31** gave

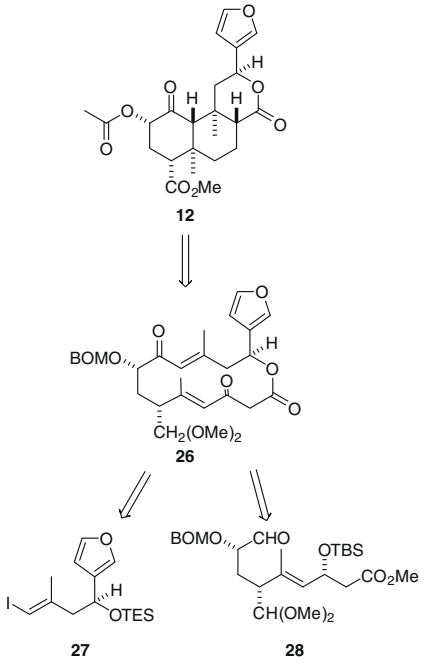
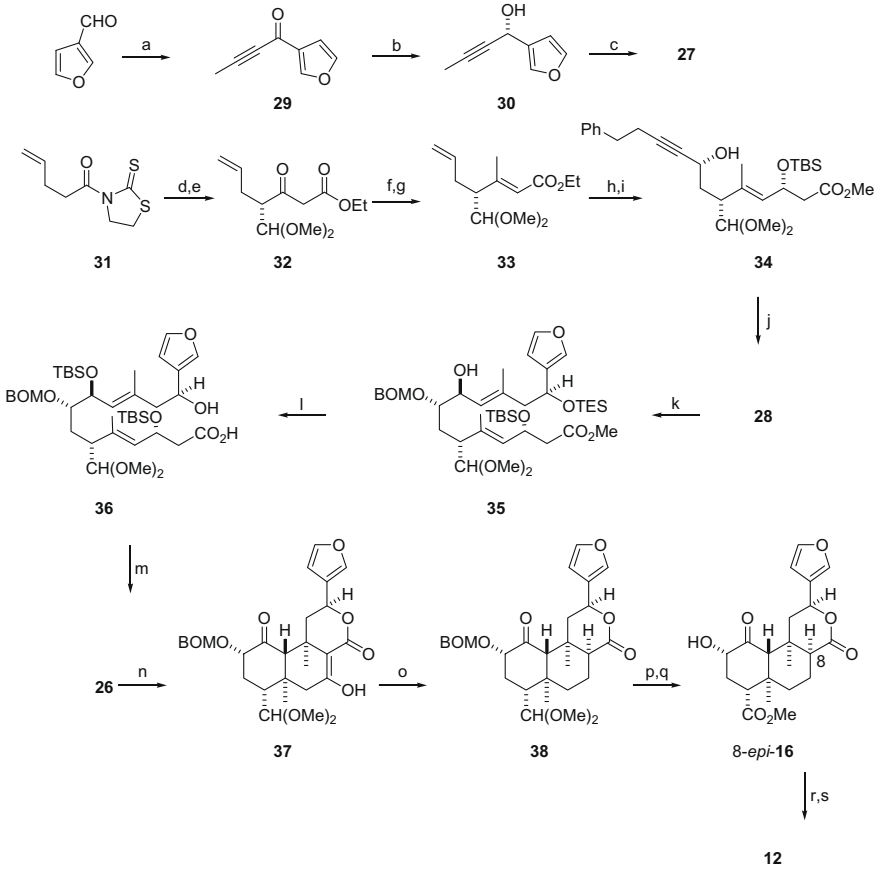


Figure 4. Retrosynthesis of **12** as proposed by Scheerer et al.[50]

the β-ketoester **32** in 85% yield. Selective formation of the (*Z*) enol phosphate using lithium hexamethyldisilazide and $ClPO(OEt)_2$ followed by Fe-catalzyed cross-coupling gave olefin **33** in 92% yield. Aldol addition, alcohol protection and acetylide addition yielded propargylyic 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 triflate 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 K_2CO_3 in CH_3OH, 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 (Fig. 5). Protection of the (*R*)- (−)-Wieland-Miescher ketone[59] followed by treatment with NH_4Cl in KOH and CH_3OH gave the hydroxy-ketone **39** in 73% yield



Scheme 1. Synthesis of **12** by Scheerer et al.[50] Reagents and conditions: (a) propyne, *n*-BuLi, Et_2O, −78 °C; (b) (*R*)-β-methyl-CBS catalyst, $BH_3{\cdot}Me_2S$, −30 °C; (c):(1) KH, $H_2N(CH_2)_3NH_2$, 0 °C; (2) Me_3Al, $Cp_{-2}ZrCl_2$, I_2, −45 °C; (3) TESCl, imidazole; (d) Ni-(*R*)-BINAP$(OTf)_2$, 2,6-lutidine, $BF_3{\cdot}OEt_2$, $HC(OMe)_3$; (e) $HO_2CCH_2CO_2Et$, *i*-PrMgCl, 65 °C; (f) LiHMDS; $ClPO(OEt)_2$; (g) $Fe(acac)_3$, MeMgCl, −20 °C; (h):(1) DIBAL-H, −78 °C; (2) MnO_2; (3) $Sn(OTf)_2$, *N*-ethylpiperidine, chiral auxiliary, −78 °C; (i): (1) TBSOTf, 2,6-lutidine; (2) K_2CO_3, CH_3OH; (3) OsO_4, NMO, $NaIO_4$; (4) $Zn(OTf)_2$, (−)-*N*-methyl-ephedrine, Et_3N, 4-phenyl-1-butyne; (j):(1) BOMCl, NaHMDS, −78 °C; (2) lindlar catalyst, H_2; (3) K_2OsO_4, NMO, citric acid, 50 °C, $Pb(OAc)_4$, K_2CO_3; (k) **27**, *n*-BuLi, $MgBr{\cdot}OEt_2$, CH_2Cl_2, −78 °C to 0 °C; (l): (1) TBSOTf, 2,6-lutidine; (2) PPTS, CH_3OH; (3) LiOH, *i*-PrOH, H_2O; (m):(1) MNBA, DMAP, [0.0015 M]; (2) TBAF; (3) Dess–Martin periodinane; (n) TBAF, −78 °C to 5 °C; (o): (1) NaH, Comins reagent; (2) $Pd(OAc)_2$, dppf, Et_3SiH; (3) L-selectride, *t*-BuOH, −78 °C to −55 °C; (p) $LiBF_4$, acetonitrile/H_2O; (q) $NaClO_2$, $TMSCHN_2$; (r) K_2CO_3, CH_3OH; (s) Ac_2O, pyridine, DMAP.

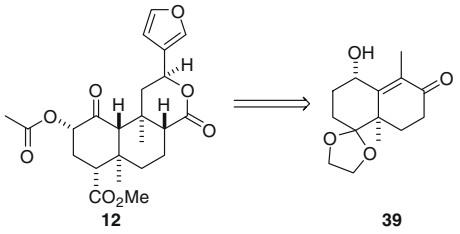
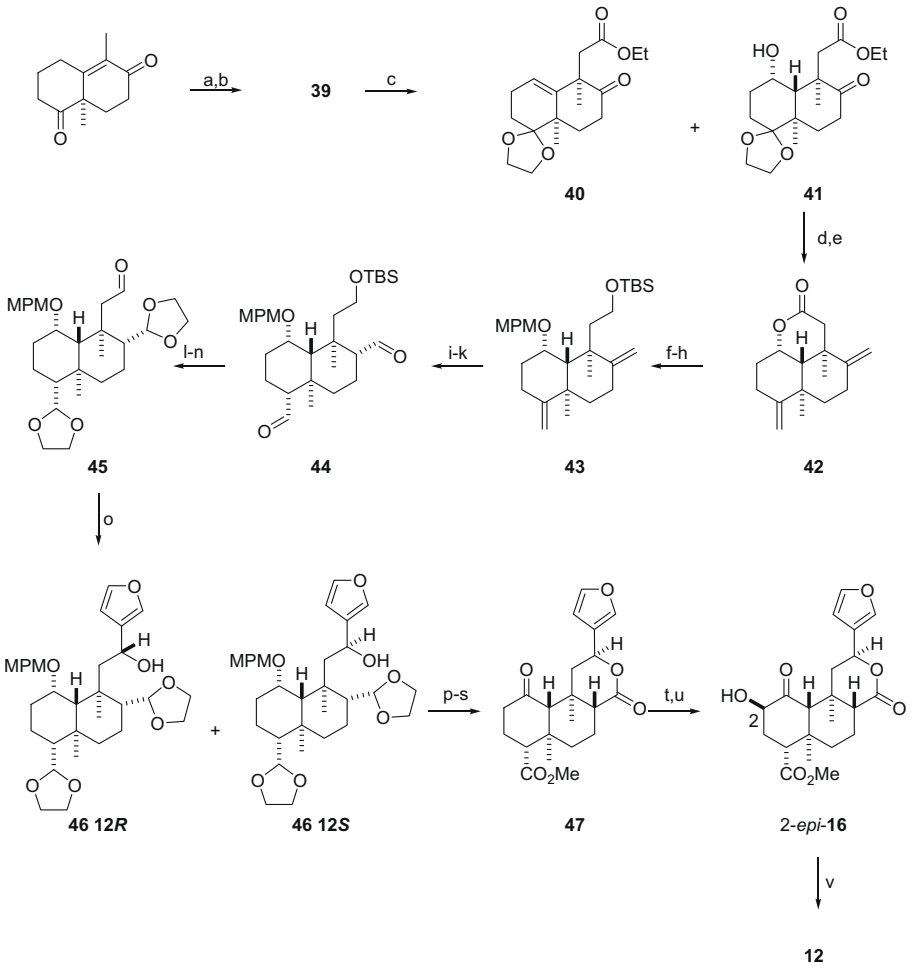


Figure 5. Retrosynthesis of **12** as proposed by Nozawa et al.[51]

(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[60] with NaHMDS and Ph_3PCH_3Br 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 12*S* furylalcohol **46** and its 12*R* 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[62] 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_2CO_3 and CH_3OH. 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.



Scheme 2. Synthesis of **12** by Nozawa et al.[51] Reagents and conditions: (a) $(CH_2)_2(OTMS)_2$, Me_3SiOTf, 15 Kbar, 40 °C; (b) KOH, CH_3OH/H_2O, 65 °C; (c) Li/NH_3, THF, −78 °C, alkyl iodide; (d) 3 M HCl aqueous EtOH; (e) NaHMDS, Ph_3PCH_3Br, THF; (f) LAH, Et_2O, 0 °C; (g) TBSCl, DMAP, Et_3N, CH_2Cl_2; (h) NaH, MPMCl, DMF; (i) BH_3, tetrahydrofuran, 3 M NaOH, H_2O_2; (j) PDC, AcONa, MS-4 Å, CH_2Cl_2; (k) NaOMe, CH_3OH; (l) ethylene glycol, PTSA, 40 °C; (m) TBAF, THF; (n) PDC, AcONa, MS-4 Å, CH_2Cl_2; (o) 3-bromofuran, *t*-BuLi, THF, −78 °C; (p) PTSA, acetone, H_2O, reflux; (q) DDQ, H_2O, CH_2Cl_2, 0 °C; (r) PDC, 2-methyl-2-butene, DMF; (s) DCC, DMAP, CH_3OH, CH_2Cl_2; (t) NaHMDS, TESCl, THF; (u) *m*-CPBA, $NaHCO_3$, toluene, H_2O, 0 °C, AcOH; (v) PPh_3, DIAD, AcOH, CH_2Cl_2.

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