



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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Chemical methods for the synthesis and modification of neoclerodane diterpenes

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ARTICLE INFO

Article history:

Received 14 May 2009

Revised 9 July 2009

Accepted 14 July 2009

Available online 17 July 2009

Keywords:

Diterpene

Neoclerodane

Salvinorin A

Salvia divinorum

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**.

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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 properties¹² and clerodidin (**6**), isolated from *Oridiodendron 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 clerodidin (**8**).² Neoclerodane

8, displays antifeedant properties and inhibits insect growth.¹⁵ These attributes have also been seen in other neoclerodanes such as ajugatanin A (**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 deterrent^{17,18} and a repellent 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 [1-¹³C;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 (Fig. 2).^{30–32,34,35} Epimerization at this center has shown to have great impact on biological activity.^{26,34,37–39} Despite

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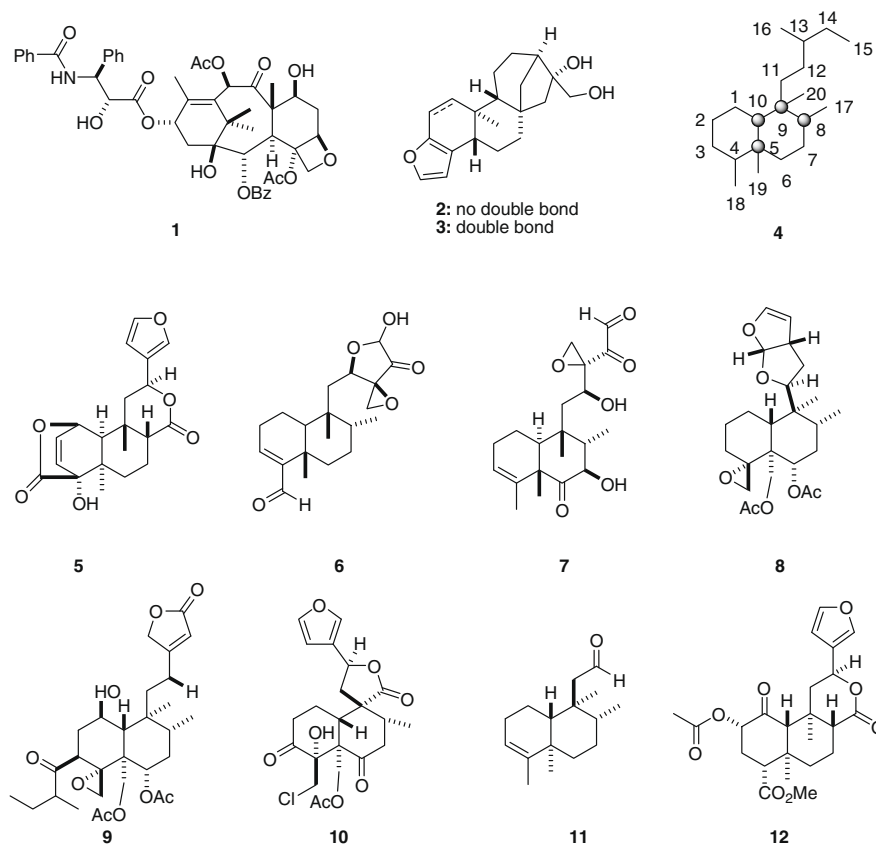


Figure 1. Structures of taxol (**1**), cafestol (**2**), kahweol (**3**), diterpene skeleton (**4**), columbin (**5**), clerocidin (**6**), terpentecin (**7**), neoclerodanes clerodin (**8**), ajugatansin A1 (**9**), traficanin A (**10**), callicarpenal (**11**) and salvinorin A (**12**).

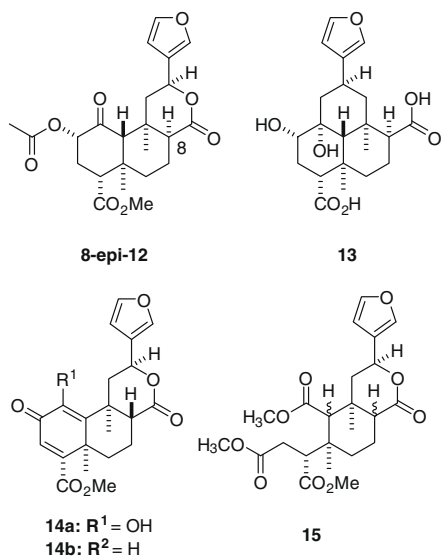


Figure 2. Compounds obtained through basic hydrolysis of **12**.

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 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

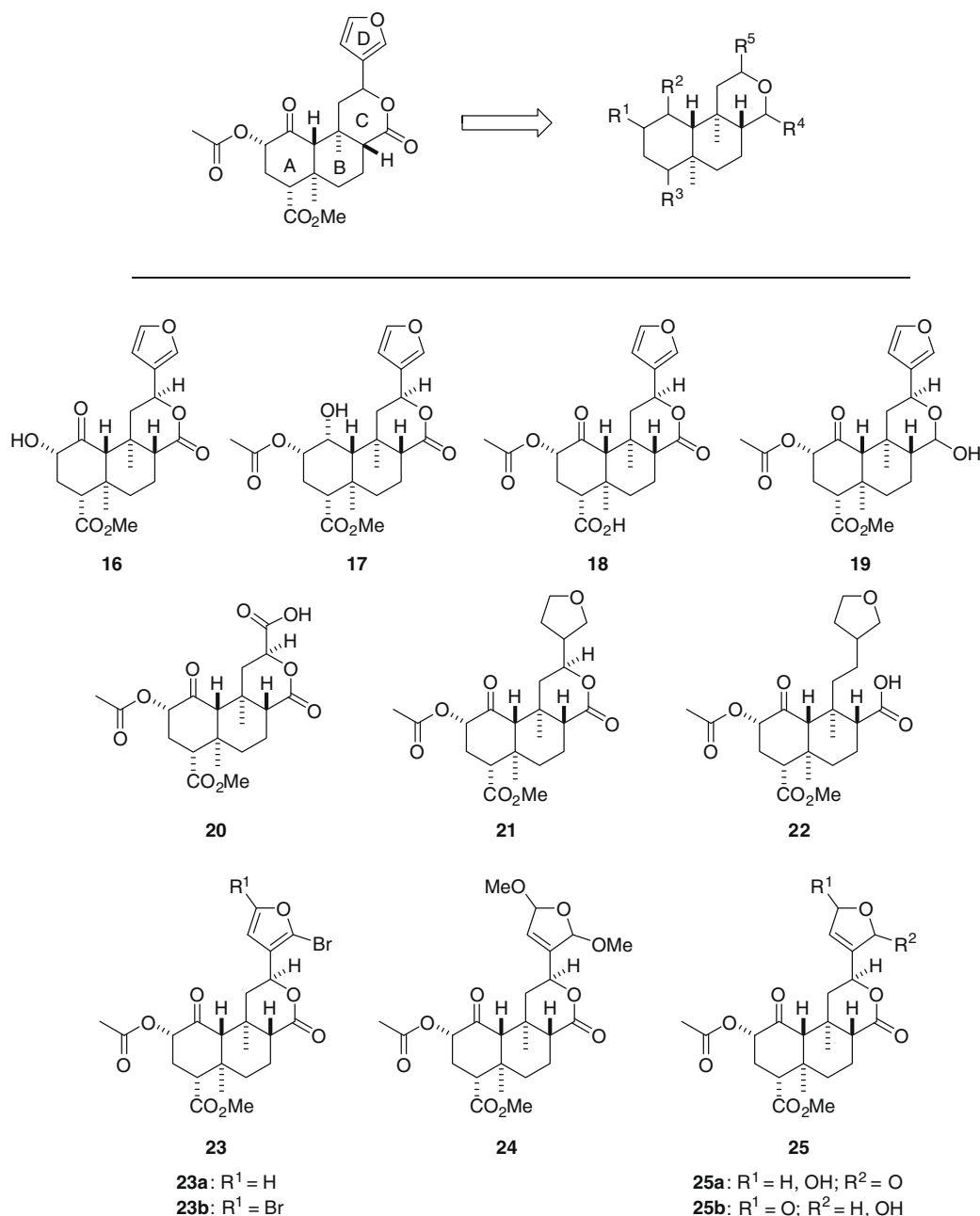
using KCN in refluxing CH₃OH/tetrahydrofuran.⁴² While this method was able to remove the acetate, it led to epimerization at C8 as the major product with 51% yield. Selective removal of the C2 acetate of **12** was accomplished in 77% yield using Na₂CO₃ in CH₃OH,³⁰ yielding salvinorin B (**16**) (Fig. 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**.^{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.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 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 DMPU 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 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 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**

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*-bromosuccinimide (NBS) in acetonitrile⁴⁶ or CHCl₃⁴⁰ 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 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 (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 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

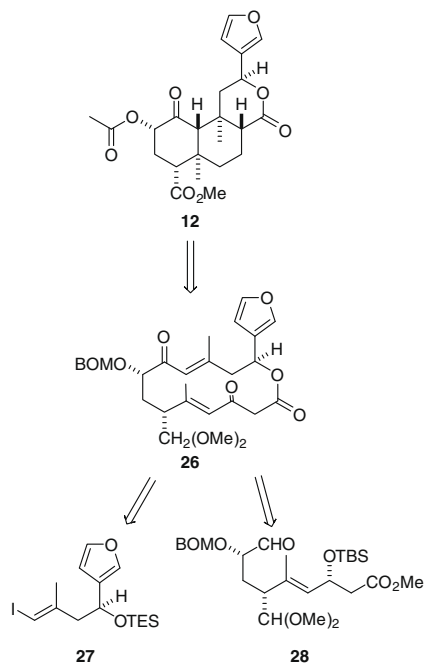
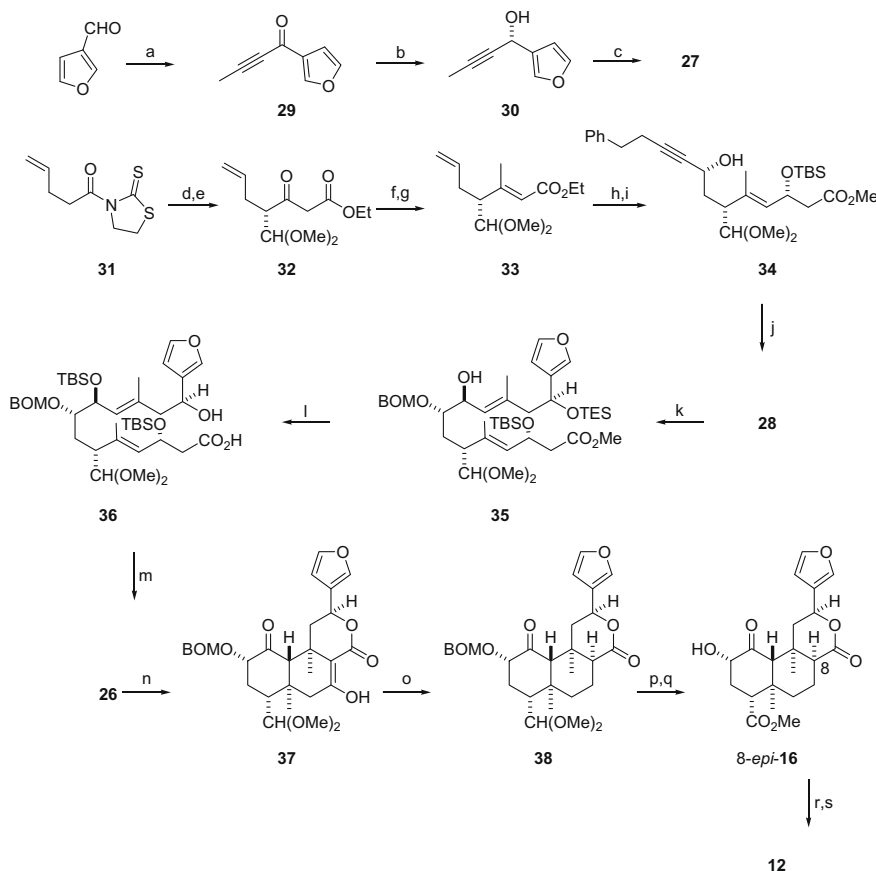


Figure 4. Retrosynthesis of **12** as proposed by Scheerer et al.⁵⁰

the β -ketoester **32** in 85% yield. Selective formation of the (*Z*) enol phosphate using lithium hexamethyldisilazide and $\text{ClPO}(\text{OEt})_2$ followed by Fe-catalyzed cross-coupling gave olefin **33** in 92% yield. Aldol addition, alcohol protection and acetylide 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 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 ketone⁵⁹ 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, $\text{BH}_3\cdot\text{Me}_2\text{S}$, -30°C ; (c): (1) KH, $\text{H}_2\text{N}(\text{CH}_2)_3\text{NH}_2$, 0°C ; (2) Me_3Al , $\text{Cp}^*_2\text{ZrCl}_2$, I_2 , -45°C ; (3) TESCl, imidazole; (d) Ni-(*R*)-BINAP(OTf)₂, 2,6-lutidine, $\text{BF}_3\cdot\text{OEt}_2$, $\text{HC}(\text{OMe})_3$; (e) $\text{HO}_2\text{CCH}_2\text{CO}_2\text{Et}$, *i*-PrMgCl, 65°C ; (f) LiHMDS; $\text{ClPO}(\text{OEt})_2$; (g) $\text{Fe}(\text{acac})_3$, MeMgCl , -20°C ; (h): (1) DIBAL-H, -78°C ; (2) MnO_2 ; (3) $\text{Sn}(\text{OTf})_2$, *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) $\text{Zn}(\text{OTf})_2$, (–)-*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 , $\text{Pb}(\text{OAc})_4$, K_2CO_3 ; (k) **27**, *n*-BuLi, $\text{MgBr}\cdot\text{OEt}_2$, 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) $\text{Pd}(\text{OAc})_2$, 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.

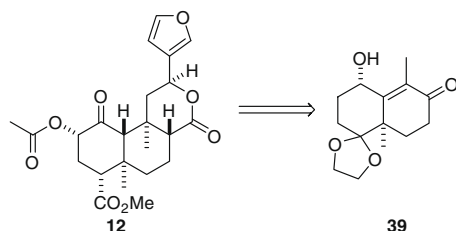
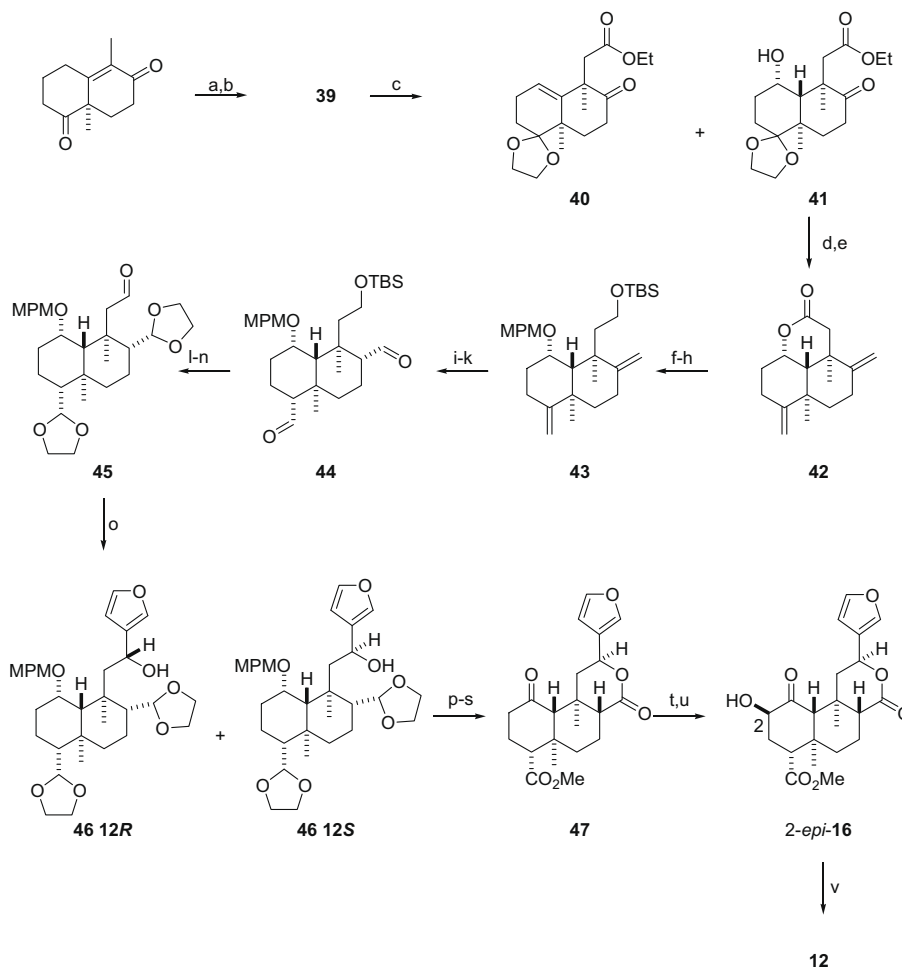


Figure 5. Retrosynthesis of **12** as proposed by Nozawa et al.⁵¹

(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 methylenation⁶⁰ with NaHMDS and Ph₃PCH₃Br 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 furalcohol **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 conditions⁶² 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 Na₂CO₃ and CH₃OH. 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) (CH₂)₂(OTMS)₂, Me₃SiOTf, 15 Kbar, 40 °C; (b) KOH, CH₃OH/H₂O, 65 °C; (c) Li/NH₃, THF, -78° C, alkyl iodide; (d) 3 M HCl aqueous EtOH; (e) NaHMDS, Ph₃PCH₃Br, THF; (f) LAH, Et₂O, 0 °C; (g) TBSCl, DMAP, Et₃N, CH₂Cl₂; (h) NaH, MPMCl, DMF; (i) BH₃, tetrahydrofuran, 3 M NaOH, H₂O₂; (j) PDC, AcONa, MS-4 Å, CH₂Cl₂; (k) NaOMe, CH₃OH; (l) ethylene glycol, PTSA, 40 °C; (m) TBAF, THF; (n) PDC, AcONa, MS-4 Å, CH₂Cl₂; (o) 3-bromofuran, *t*-BuLi, THF, -78° C; (p) PTSA, acetone, H₂O, reflux; (q) DDQ, H₂O, CH₂Cl₂, 0 °C; (r) PDC, 2-methyl-2-butene, DMF; (s) DCC, DMAP, CH₃OH, CH₂Cl₂; (t) NaHMDS, TESCl, THF; (u) *m*-CPBA, NaHCO₃, toluene, H₂O, 0 °C, AcOH; (v) PPh₃, DIAD, AcOH, CH₂Cl₂.

Acknowledgements

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. A.L. is currently supported by NIDA grant DA018151S1.

References and notes

- Ruzicka, L. *Experientia* **1953**, 9, 357.
- Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, 9, 243.
- Eisenreich, W.; Bacher, A.; Arigoni, D.; Rohdich, F. *Cell. Mol. Life Sci.* **2004**, 61, 1401.
- Eisenreich, W.; Rohdich, F.; Bacher, A. *Trends Plant Sci.* **2001**, 6, 78.
- Silver, G. M.; Fall, R. J. *Biol. Chem.* **1995**, 270, 13010.
- Koepp, A. E.; Hezari, M.; Zajicek, J.; Vogel, B. S.; LaFever, R. E.; Lewis, N. G.; Croteau, R. J. *Biol. Chem.* **1995**, 270, 8686.
- Cavin, C.; Holzhaeuser, D.; Scharf, G.; Constable, A.; Huber, W. W.; Schilter, B. *Food Chem. Toxicol.* **2002**, 40, 1155.
- Wattenberg, L. W.; Hanley, A. B.; Barany, G.; Spamins, V. L.; Lam, L. K.; Fenwick, G. R. *Int. Symp. Princess Takamatsu Cancer Res. Fund* **1985**, 16, 193.
- Tokoroyama, T. *Synthesis* **2000**, 5, 611.
- De la Torre, M. C.; Hueso-Rodriguez, J. A.; Rodriguez, B.; Servettaz, O.; Piozzi, F.; Savona, G. *Phytochemistry* **1986**, 25, 2239.
- Barton, D. H. R.; Elad, D. J. *Chem. Soc.* **1956**, 2085.
- Kohno, H.; Maeda, M.; Tanino, M.; Tsukio, Y.; Ueda, N.; Wada, K.; Sugie, S.; Mori, H.; Tanaka, T. *Cancer Lett.* **2002**, 183, 131.
- Andersen, N. R.; Lorch, H. O. B.; Rasmussen, P. R. J. *Antibiot.* **1983**, 36, 753.
- Kawada, S.; Yamashita, Y.; Ochiai, K.; Ando, K.; Iwasaki, T.; Takiguchi, T.; Nakano, H. J. *Antibiot.* **1995**, 48, 211.
- Krishna Kumari, G. N.; Balachandran, J.; Aravind, S.; Ganesh, M. R. J. *Agric. Food. Chem.* **2003**, 51, 1555.
- Jain, D. C.; Tripathi, A. K. *Phytother. Res.* **1993**, 7, 327.
- Cantrell, C. L.; Klun, J. A.; Bryson, C. T.; Kobaisy, M.; Duke, S. O. J. *Agric. Food. Chem.* **2005**, 53, 5948.
- Cantrell, C. L.; Klun, J. A.; Pridgeon, J.; Becnel, J.; Green, S., 3rd; Fronczek, F. R. *Chem. Biodivers.* **2009**, 6, 447.
- Carroll, J. F.; Cantrell, C. L.; Klun, J. A.; Kramer, M. *Exp. Appl. Acarol.* **2007**, 41, 215.
- Hagiwara, H.; Hamano, K.; Nozawa, M.; Hoshi, T.; Suzuki, T.; Kido, F. J. *Org. Chem.* **2005**, 70, 2250.
- Xiang, A. X.; Watson, D. A.; Ling, T.; Theodorakis, E. A. J. *Org. Chem.* **1998**, 63, 6774.
- Grossman, R. B.; Rasne, R. M. *Org. Lett.* **2001**, 3, 4027.
- Valdes, L. J., 3rd; Diaz, J. L.; Paul, A. G. J. *Ethnopharmacol.* **1983**, 7, 287.
- Valdes, L. J., 3rd J. *Nat. Prod.* **1986**, 49, 171.
- Siebert, D. J. J. *Ethnopharmacol.* **1994**, 43, 53.
- Valdes, L. J., 3rd J. *Psychoactive Drugs* **1994**, 26, 277.
- Prisinzano, T. E. *Life Sci.* **2005**, 78, 527.
- Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernberger, P.; Rothman, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, 99, 11934.
- Prisinzano, T. E.; Tidgewell, K.; Harding, W. W. *AAPS J.* **2005**, 7, E592.
- Tidgewell, K.; Harding, W. W.; Schmidt, M.; Holden, K. G.; Murry, D. J.; Prisinzano, T. E. *Bioorg. Med. Chem. Lett.* **2004**, 14, 5099.
- Beguín, C.; Richards, M. R.; Wang, Y.; Chen, Y.; Liu-Chen, L. Y.; Ma, Z.; Lee, D. Y.; Carlezon, W. A., Jr.; Cohen, B. M. *Bioorg. Med. Chem. Lett.* **2005**, 15, 2761.
- Harding, W. W.; Tidgewell, K.; Byrd, N.; Cobb, H.; Dersch, C. M.; Butelman, E. R.; Rothman, R. B.; Prisinzano, T. E. J. *Med. Chem.* **2005**, 48, 4765.
- Harding, W. W.; Tidgewell, K.; Schmidt, M.; Shah, K.; Dersch, C. M.; Snyder, J.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. *Org. Lett.* **2005**, 7, 3017.
- Lee, D. Y.; Karnati, V. V.; He, M.; Liu-Chen, L. Y.; Kondaveti, L.; Ma, Z.; Wang, Y.; Chen, Y.; Beguin, C.; Carlezon, W. A., Jr.; Cohen, B. *Bioorg. Med. Chem. Lett.* **2005**, 15, 3744.
- Munro, T. A.; Goetchius, G. W.; Roth, B. L.; Vortherms, T. A.; Rizzacasa, M. A. J. *Org. Chem.* **2005**, 70, 10057.
- Kutrzeba, L.; Dayan, F. E.; Howell, J. L.; Feng, J.; Giner, J.-L.; Zjawiony, J. K. *Phytochemistry* **2007**, 68, 1872.
- Munro, T. A.; Rizzacasa, M. A.; Roth, B. L.; Toth, B. A.; Yan, F. J. *Med. Chem.* **2005**, 48, 345.
- Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Gilmour, B.; Navarro, H.; Rothman, R. B.; Prisinzano, T. E. J. *Nat. Prod.* **2006**, 69, 107.
- Tidgewell, K.; Harding, W. W.; Lozama, A.; Cobb, H.; Shah, K.; Kannan, P.; Dersch, C. M.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. J. *Nat. Prod.* **2006**, 69, 914.
- Beguín, C.; Duncan, K. K.; Munro, T. A.; Ho, D. M.; Xu, W.; Liu-Chen, L. Y.; Carlezon, W. A., Jr.; Cohen, B. M. *Bioorg. Med. Chem. Lett.* **2009**, 17, 1370.
- Bikbulatov, R. V.; Yan, F.; Roth, B. L.; Zjawiony, J. K. *Bioorg. Med. Chem. Lett.* **2007**, 17, 2229.
- Brown, L. 1984.
- Valdes, L. J., 3rd; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. J. *Org. Chem.* **1984**, 49, 4716.
- Holden, K. G.; Tidgewell, K.; Marquam, A.; Rothman, R. B.; Navarro, H.; Prisinzano, T. E. *Bioorg. Med. Chem. Lett.* **2007**, 17, 6111.
- Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Dersch, C. M.; Rothman, R. B.; Prisinzano, T. E. *Bioorg. Med. Chem. Lett.* **2006**, 16, 3170.
- Simpson, D. S.; Katavic, P. L.; Lozama, A.; Harding, W. W.; Parrish, D.; Deschamps, J. R.; Dersch, C. M.; Partilla, J. S.; Rothman, R. B.; Navarro, H.; Prisinzano, T. E. J. *Med. Chem.* **2007**, 50, 3596.
- Lozama, A.; Prisinzano, T. E. *Unpublished results*, 2009.
- Prisinzano, T. E.; Rothman, R. B. *Chem. Rev.* **2008**, 108, 1732.
- Bergman, Y. E.; Mulder, R.; Perlmutter, P. J. *Org. Chem.* **2009**, 74, 2589.
- Lingham, A. R.; Hügel, H. M.; Rook, T. J. *Aust. J. Chem.* **2006**, 59, 340.
- Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. J. *Am. Chem. Soc.* **2007**, 129, 8968.
- Nozawa, M.; Suka, Y.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2008**, 10, 1365.
- Burns, A. C.; Forsyth, C. J. *Org. Lett.* **2008**, 10, 97.
- Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, 41, 4569.
- Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, 41, 4573.
- Ho, T. *Tandem Org. React.* **1992**, 33.
- Claisen, L. *Ber. Deutsch. Chem. Ges.* **1881**, 14, 2460.
- Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, 43, 7535.
- Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, 33, 2215.
- Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, 87, 1318.
- Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 15, 4319.
- But, T. Y.; Toy, P. H. J. *Am. Chem. Soc.* **2006**, 128, 9636.