Pergamon

Tetrahedron Vol. 51, No. 20, pp. 5847-5870, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00237-5

A Stereo- and Enantioselective Approach to Clavulones from Tricyclodecadienone using Flash Vacuum Thermolysis

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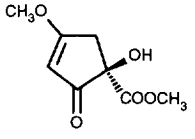
***Abstract**: The stereo- and enantioselective synthesis of clavulones **6** and their analogues **48** is described. γ-Hydroxycyclopentenones (-)-**13** and **44**, which are key intermediates in this approach, are obtained from enantiopure* endo-*tricyclo[5.2.1.0^{2,6}]decadienones (+)-**14** and (+)-**20** in 6 and 8 steps, respectively. Crucial steps are the reductive epoxy ring opening in compounds (+)-**25** and **39** to give the corresponding diols (+)-**27** and **40**, and the thermal cycloreversion of tricyclodecenones (+)-**27** and **41**, using the technique of flash vacuum thermolysis (FVT). The synthesis of enantiopure (-)-**13** represents a formal total synthesis of clavulones **6**. The synthesis of clavulone analogues (-)-**48E** and (-)-**48Z** (X= CH_2OH) is completed by condensation of **44** with aldehyde **45** followed by elimination of water and removal of the protective THP-group.*

Introduction

Natural products containing the cyclopentanone or cyclopentenone substructure generally show significant biological activity. The pharmacological importance of cyclopentanoids was especially recognized in the early 1960s when prostaglandins were isolated and shown to be essential human fatty acid hormones that control a multitude of important physiological processes[1]. Later, other biologically



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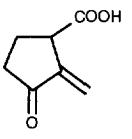

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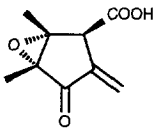

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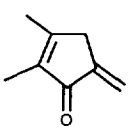

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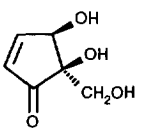

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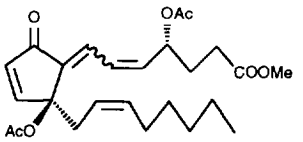

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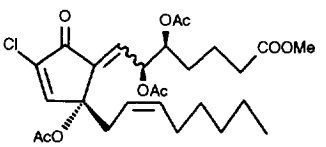

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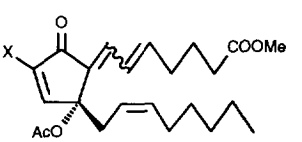

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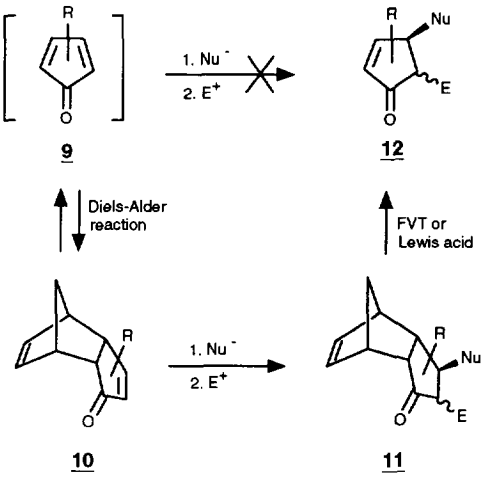
interesting cyclopentanoids were discovered which possess antibiotic and/or antitumor activity[2].

Examples are kjellmanianone **1**[2b], sarkomycin **2**[2c], methylenomycins A **3** and B **4**[2d], pentenomycin **5**[2e], and a series of marine eicosanoids related to prostaglandins, such as clavulones **6**[3], punaglandins **7**[4] and halovulones **8**[5] (X= Cl, Br and I). These discoveries initiated enormous synthetic activity aimed at developing effective stereo- and enantioselective methods for the construction of highly functionalized cyclopentanoids[6-8].

A most direct route to these compounds would involve the chemical transformation of appropriately substituted cyclopentadienones **9**, *e.g.* by conjugate addition of suitable nucleophiles followed by electrophilic trapping of the enolate (Scheme 1). This approach, however, is not feasible as

Scheme 1

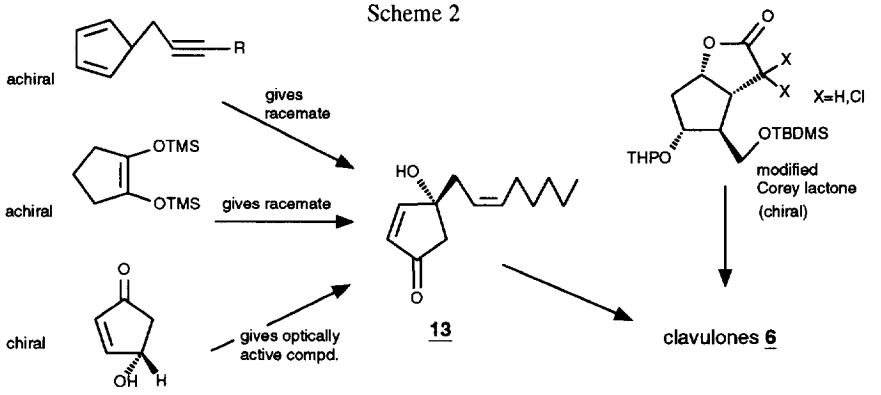


cyclopentadienones **9** are highly reactive molecules[9] which generally dimerize at temperatures above -100 °C. Therefore, the *endo*-tricyclo[5.2.1.$0^{2,6}$]decadienone system **10** was explored as a synthetic equivalent of cyclopentadienones **9**. In recent years, it has been demonstrated that this system is an extremely useful synthon for a great variety of naturally occurring cyclopentanoids. These tricyclodecadienones **10**, which essentially are the Diels-Alder adducts of cyclopentadienones with cyclopentadiene, can be considered as cyclopentadienones **9** in which one of the double bonds is protected. Chemical transformation of the remaining enone system, *e.g.* by nucleophilic addition and/or electrophilic substitution, followed by a retro Diels-Alder reaction of **11** induced by Lewis acid or thermolysis using the Flash Vacuum Thermolysis (FVT) technique regenerates this masked enone function to yield functionalized cyclopentenones **12**. The success of this approach is primarily due to two factors, *viz.* (i) the ready availability of *endo*-tricyclodecadienones **10** (R= COOEt and H) of which both enantiopure antipodes can be obtained by enzymatic resolution of one of its precursors[8b,10,11], and (ii) the high regio- and stereoselectivity observed for the 1,2- and 1,4-addition of nucleophiles to the enone moiety[12]. This stereoselectivity is attributed to the steric hindrance of the concave *endo*-face in **10** (when R= H, this effect is almost completely preponderant). This synthetic strategy has successfully been applied by the Nijmegen research group[7] and others[8] for the synthesis of a great variety of naturally occurring cyclopentanoids or pharmacologically important structures. This paper[13] describes the stereospecific formal synthesis of clavulones **6** and the preparation of some analogues **48** using this strategy.

Stereospecific preparation of key intermediate 13 for the total synthesis of clavulones

Clavulones **6** are a new class of prostanoid, which were isolated from marine origin in 1982[3] and shown to have strong antitumor activities. In the past few years, the synthesis of these marine prostanoids has been accomplished in racemic form as well with the natural configuration[14]. In these synthetic approaches[14a-c] precusor **13** is used as the key intermediate (Scheme 2). Also a clavulone synthesis is

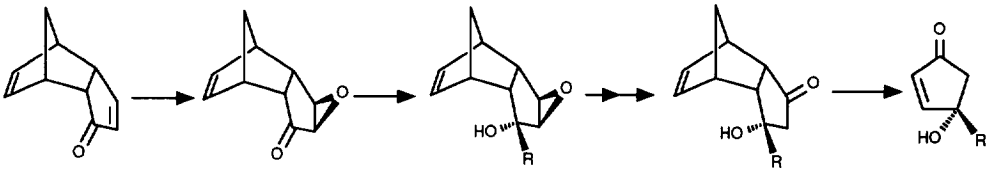
Scheme 2



known[14d,e] which starts from the Corey lactone, the well known prostaglandin intermediate. Among the syntheses shown in Scheme 2, only Yamada's route[14b] proceeds *via* intermediate **13** in optically active but not enantiopure form (the enantiopurity is *ca.* 64%, *vide infra*). In this paper, a stereospecific synthesis of the key intermediate **13** is described, which can be used for the complete enantiospecific synthesis of clavulones.

It has previously been demonstrated[15] that tricyclic epoxy ketone **15** undergoes a regio- and stereoselective nucleophilic addition with both metal hydrides and organolithium compounds to form epoxy *endo*-alcohols **16**. The present approach to clavulones is based on the observation (Scheme 3) that nucleophilic addition to epoxy ketone **15** will take place preferentially from the convex side of the molecule. Subsequent reductive epoxy opening, selective oxidation of the secondary alcohol function and thermal cycloreversion will ultimately lead to 4-hydroxycyclopentenone **13**, which is the key intermediate mentioned above.

Scheme 3



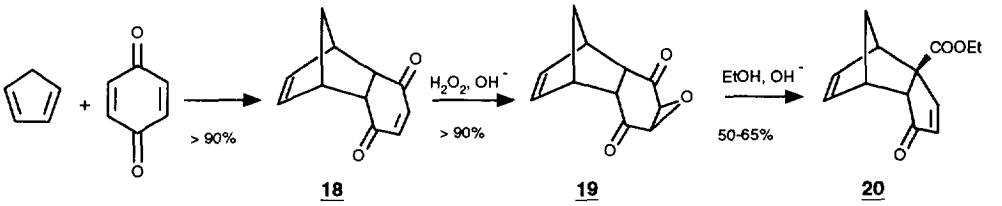
14 **15** **16** **17** **13**

For the synthesis of enantiopure parent *endo*-tricyclodecadienone **14**, which is the pivotal starting material in this strategy, three practical methods have been reported so far. They are based on the enzymatic enantioselective hydrolysis or esterification of a suitable tricyclodecenyl precursor[8b,10,11]. One

of the most efficient routes, which was reported by the Nijmegen group[10], involves the kinetic resolution of enone ester **20** using pig liver esterase (PLE). Enantiopure **20**, which is not obtainable by the other two methods, is also the starting material for the synthesis of some clavulone analogues (*vide infra*).

Racemic tricyclic ethyl ester **20** can easily be obtained by selective epoxidation of the enone moiety in Diels-Alder adduct **18** of cyclopentadiene and p-benzoquinone, followed by a Favorskii ring contraction of the resulting tricyclic epoxide **19** as shown in Scheme 4[10]. Treatment of racemic tricyclic ethyl ester **20**

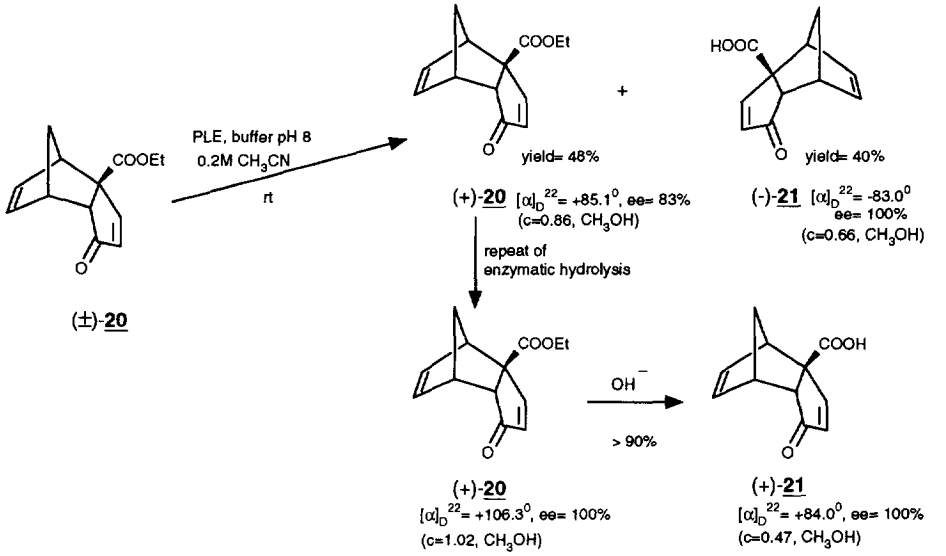
Scheme 4



18 **19** **20**

with PLE at room temperature in a 0.1M phosphate buffer (pH 8.0) containing acetonitrile as the co-solvent, resulted in a slow hydrolysis to give carboxylic acid (-)-**21** in excellent chemical yield and with a high enantiopurity. The enantiopurity could be further improved by crystallization (Scheme 5). Ester

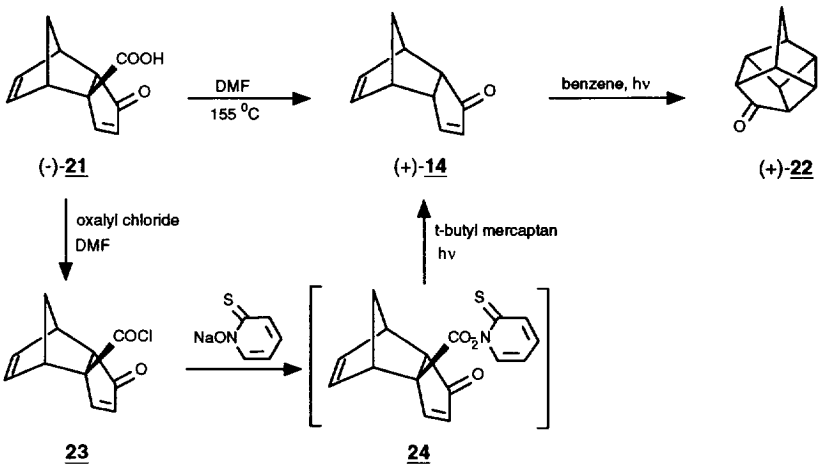
Scheme 5



(+)-**20** was obtained during this enzymatic process as the remaining ester which, after repeated enzymatic hydrolysis followed by alkaline hydrolysis, gave enantiopure antipode (+)-**21**. In order to determine the enantiopurity of ester **20** and acid **21**, the tricyclic structure (-)-**21** was correlated with a known optically active compound, *viz.* 1,3-bishomocubanone (+)-**22**, which has been prepared by Nakazaki[16]. Its absolute configuration was determined by using CD spectroscopy.

The conversion of (-)-**21** into cage ketone (+)-**22** was accomplished by photo-ring closure after decarboxylation as depicted in Scheme 6. The vinylogous β-ketoacid, (-)-**21** ($[\alpha]_D^{22}$= -83°, c=0.66,

Scheme 6

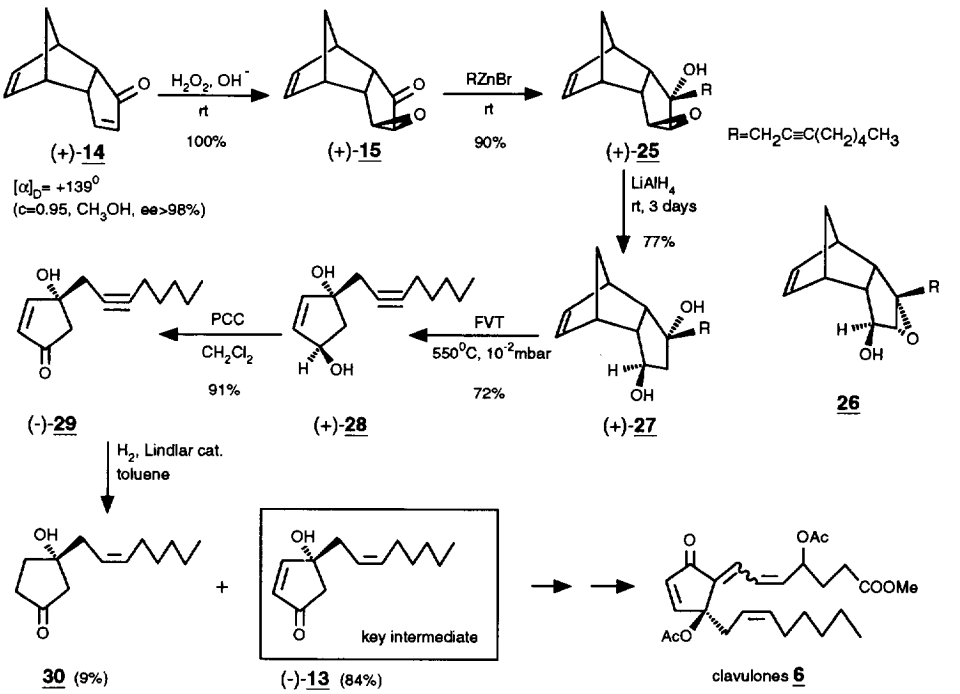


CH_3OH) was readily decarboxylated by heating in dimethylformamide at 155°C to give the parent tricyclodecadienone **14** ($[\alpha]_D^{22}$= +141.2°, c=0.68, CH_3OH, after recrystallization from hexane), in 83% yield. Intramolecular photochemical cyclization of (+)-**14** gave 1,3-bishomocubanone (+)-**22** in quantitative yield. Its optical rotation ($[\alpha]_D^{22}$= +11°, c=0.67, $CHCl_3$) was identical to that reported by Nakazaki *et al.*[16] Although this result strongly suggests that enantiopure (+)-**22** was obtained from optically pure tricyclic acid (+)-**14**, there is still some suspicion about the stereochemical course of the decarboxylation step (**21** to **14**). The initially obtained product (+)-**14** after flash chromatography gave an optical rotation of only 125-130°, suggesting that some racemization may have taken place during the thermal decarboxylation reaction or alternatively that the starting acid **21** was not enantiopure. In order to remove any doubt about the integrity of the decarboxylation step, the conversion of **21** into **14** was performed in an alternative manner, namely by employing Barton's radical decarboxylation method.[17] Applying this approach no racemization is feasible[8c,d]. Conversion of (-)-**21** into the corresponding acid chloride **23** followed by treatment with N-hydroxypyridin-2-thione sodium salt gave N-acyloxypyridin-2-thione **24** which was exposed to light in benzene at reflux in the presence of t-butyl mercaptan. Enantiopure (+)-**14** was obtained after column chromatography ($[\alpha]_D^{25}$= +139°, c=0.95, CH_3OH). This result proves that (-)-**21** as obtained by the enzymatic resolution is enantiopure and that as a consequence, the thermal decarboxylation of **21** must be accompanied by partial racemization (see initially obtained optical rotation). This supposition has been put foreward by Garland *et al.*[8c] who repeated the procedure described here for the decarboxylation in dimethylformamide and suggested that a process of a retro Diels-Alder and recombination reaction may be responsible for the observed racemization. Assuming that a retro Diels-Alder reaction is indeed taking place at a temperature of 155 °C, the decarboxylation of **21** was attempted at a lower temperature and a prolonged reaction time, *viz.* at 100°C for 24 hrs. This experimental condition gave a satisfactory result, as the decarboxylation product **14** now had an optical rotation of $[\alpha]_D^{25}$= +138.5°(c=0.41, CH_3OH) after column chromatography (chemical yield: 78%). The results described above indicate that during the decarboxylation at *ca.* 100°C the stereochemical integrity is retained and that the chemical transformation of (-)-**21** into (+)-**22** provides a

useful method for establishing the optical purity and absolute configuration of (-)-**21** as well as that of (+)-**14**. As parent tricyclodecadienone **14** is an important chiron in the synthesis of cyclopentenoid natural products, some further comment on its optical rotation is in place. The reports[8c,11a] about the optical rotation are rather confusing, because different solvents are used. It was found that the optical rotation of **14** exhibits a considerable solvent effect, as is exemplified by the following data: $[\alpha]_D^{25}=141.2°$ (c=0.67, CH_3OH), $[\alpha]_D^{25}=150.2°$ (c=0.53, CH_2Cl_2) and $[\alpha]_D^{25}=166.7°$(c=0.95, $CHCl_3$), respectively.

The key intermediate (-)-**13** for the clavulone synthesis was obtained from (+)-tricyclo[5.2.1.$0^{2,6}$]-decadienone (+)-**14** in six steps by the sequence of events outlined in Scheme 7. *Exo*-epoxide (+)-**15** was

Scheme 7

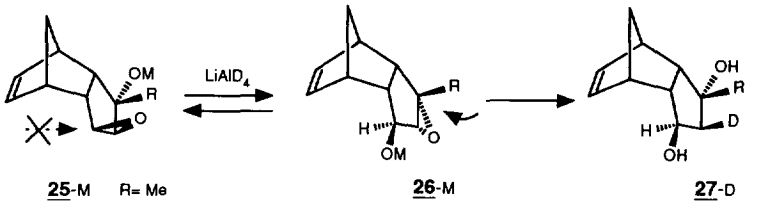


readily obtained in almost quantitative yield by treatment of (+)-**14** with hydrogen peroxide under basic conditions. Attempts to introduce the alkynyl chain into tricyclic epoxide (+)-**15** by using oct-2-ynyl magnesium bromide, unexpectedly gave a complex mixture of products containing alcohols **25** and **26** in a disappointingly low yield. A satisfactory result was obtained by applying the less reactive octynylzinc reagent. Again, attack of the organometallic reagent takes place preferentially from the convex side of the molecule. Epoxide (+)-**25** was formed as the sole product in nearly 90% yield. It is interesting to note that with zinc reagent no detectable rearranged product **26** was found, whereas similar reactions with n-butyllithium and methyllithium lead to a mixture of **25** and **26**[15].

Reduction of (+)-**25** with lithium aluminum hydride in tetrahydrofuran at room temperature for three days slowly produced the desired 1,3-diol (+)-**27** in 77% yield. This remarkable conversion of (+)-**25** into (+)-**27** can be rationalized as follows. Epoxide (+)-**25** itself cannot undergo a reductive epoxide opening as its *endo* face is sterically blocked for hydride attack by the C_8-C_9 ethylene bridge. However, the initially

formed lithium aluminum alcoholate **25**-M can undergo a Payne rearrangement[15] as the *endo* alcoholate is favorably disposed for intramolecular nucleophilic attack from the concave face of the molecule. The rearranged epoxide alcoholate **26**-M can now undergo epoxide opening by hydride attack from the readily accessible *exo* (convex) face, to give diol **27**. Support for this mechanistic course was obtained by the reaction of **25** (R=Me) with lithium aluminum deuteride which gave *exo*-deuterated diol **27**-D (R=Me)

Scheme 8



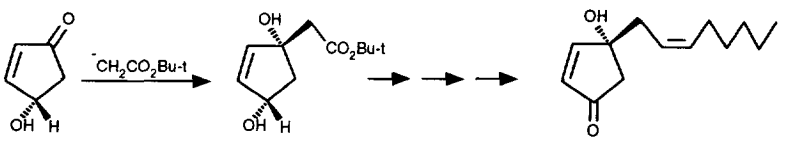
25-M R= Me **26**-M **27**-D

exclusively[16] (Scheme 8). It should be noted that this conclusion is in contrast with that recently reported by Liu[18], who claimes that direct epoxide ring-opening of **25** to afford the 3,5-diol **27** is the primary pathway.

In the subsequent step this diol (+)-**27** was subjected to thermal cycloreversion employing the flash vacuum thermolysis technique. In a smooth manner cyclopentene diol (+)-**28** was obtained in a yield of 72%. Oxidation of **28** with pyridinium chlorochromate furnished γ-hydroxy cyclopentenone (+)-**29** in almost quantitative yield. The selective hydrogenation of **29** using Lindlar catalyst strongly depended on the solvent used. The best result was obtained in toluene giving key intermediate (+)-**13** in 84% yield ($[\alpha]_D^{25}$= -84.0°, c=0.31, $CHCl_3$) (lit.[14b] $[\alpha]_D$= -54.1°, c=1.52, $CHCl_3$) along with a small amount of ring-saturated by-product **30** (9%).

Because of the considerable difference in optical rotation of compound **13** observed in the present case and that reported in the literature[14b], it is necessary to provide unambiguous information about the enantiopurity of this compound. A ^{1}HNMR spectral analysis of **13** using chiral shift reagents employing its racemate as reference material, unequivocally established that the enantiopurity of compound **13** prepared according to Scheme 7 is almost 100%. Consequently, the product **13** as prepared by Yamada[14b] in his approach to clavulones has a much lower enantiomeric purity, namely *ca.* 64%. In order to check whether Yamada's route indeed leads to a lower enantiomeric purity of **13**, this route was carefully repeated (Scheme 9). In this route the stereochemical integrity is determined in the first step which involves the reaction of the enolate of t-butyl acetate with hydroxy cyclopentenone **31**. This substrate was available with an enantiopurity of 52%[19]. Reaction of **31** with 2.2 equiv. of lithium enolate of t-butyl acetate in

Scheme 9

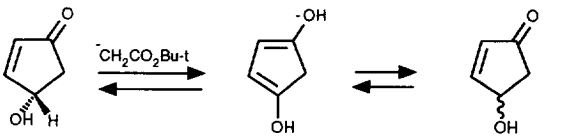


31 **32** **13**

tetrahydrofuran at -78°C for 15 min. gave diol **32** ($[\alpha]_D^{25}$= 27.7°, c=1.39, $CHCl_3$, after chromatography). A

gas chromatographic analysis showed only one peak and thin-layer chromatography gave only one spot, indicating the quantitative formation of cis-diol, as was also suggested by Yamada[14b]. However, the optical purity was still not known. Fortunately, storing cis-diol **32** in the refrigerator for two weeks gave some crystalline material, which was used for seeding purposes in the subsequent crystallization of the oily product obtained. Repeated crystallization until constant optical rotation, led to **32** as nice needle crystals (m.p.= 69.5-71°C, $[\alpha]_D^{25}$= -56.6°, c=1.32, $CHCl_3$). The optical rotation obtained for **32** is much higher than that reported by Yamada[14b] ($[\alpha]_D$= -45.9°, c=1.12, $CHCl_3$, they did not mention that it was a solid !). This result convincingly proves that the product prepared by Yamada[14b] is not enantiopure. This lesser enantiopurity can be explained by invoking a base-induced racemization of **31**, which in fact is an enolization reaction, as shown in Scheme 10.

Scheme 10



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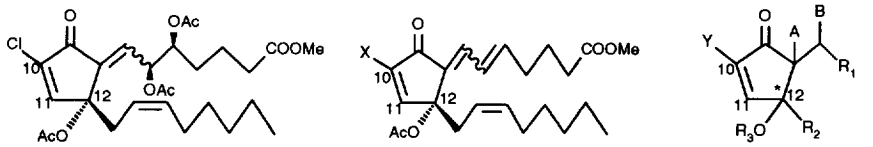
In summary the chemistry presented above clearly demonstrates that tricyclo[5.2.1.$0^{2,6}$]decadienone **14** is a useful chiron for the stereospecific synthesis of cyclopentenoids. The preparation of key intermediate **13** represents a formal total synthesis of clavulones **6**, as this intermediate has been converted into this natural product by Yamada[14b] starting from **13** with an enantiomeric excess of 64% and by Corey[14a] starting from racemic **13**.

Total synthesis of some clavulone analogues

Soon after the reports[3] on clavulones **6**, several halogenated marine prostanoids e.g. punaglandins **7**[4] and halovulones **8**[5] (X= Cl,Br,I) were isolated. The antitumor activities of these prostanoids having a halogen atom in the cyclopentenone moiety are much higher than those of clavulones **6**. In the past few years, the synthesis of some halogenated marine prostanoids has been accomplished[20]. In attempts to find a



7 **8** **33**

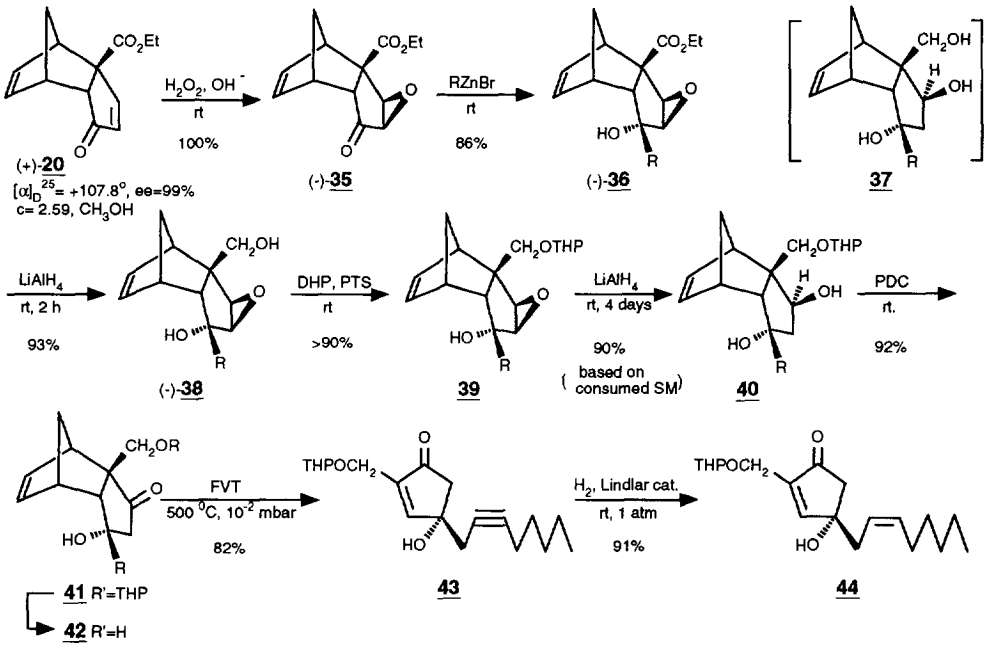
clinically useful compound, a great variety of marine prostanoid derivatives **33** has been synthesized. Most of them are reported in the Japanese patent literature[21]. Biological evaluation of these analogues of clavulones has led to the following structure-activity relationship in this class of compounds: (i) the $C_{10\text{-}11}$ olefin unit is essential for the activity, (ii) a halogen atom at C_{10} increases the activity of the clavulones, (iii) the C_{12} hydroxyl or acetate is also required for full activity[22]. It should be noted that some C_{10}-substituted analogues **33** with $Y=S(O)_nR$ showed significant anticancer activity and bone formation promotion[21d]. In view of the apparent higher antitumor activity of C_{10}-substituted clavulone analogues,

the synthesis and biological evaluation of clavulones with a modified substituent at C_{10} is clearly of interest. In this paper an effective approach to C_{10}-hydroxymethyl substituted analogues is described.

Retrosynthetic analysis of these target molecules indicates that by employing the strategy as depicted in Scheme 1, this structural modification at C_{10} in clavulone-type compounds can be achieved when 6-functionalized tricyclodecadienone **20** is used instead of the parent synthon **14**. This approach, if successful, will expand the synthetic merits of the tricyclodecadienone system.

The stereoselective synthesis of hydroxymethyl precursor **44** for modified marine prostanoids is depicted in Scheme 11. This sequence of events involves chemical transformation of the ethoxycarbonyl

Scheme 11



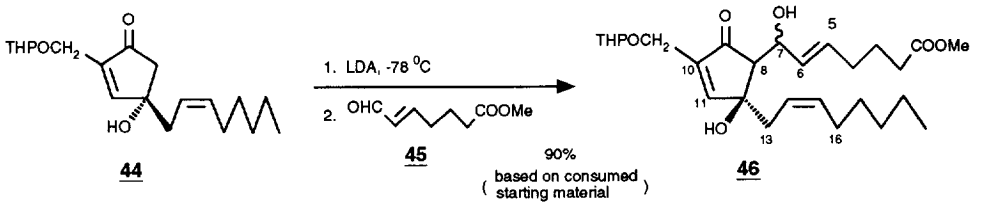
group at C_6 in tricyclodecadienone[23], which in this case is a reduction to the hydroxymethyl group by brief treatment of compound **36** with lithium aluminum hydride. Protection of the thus obtained alcohol function as a tetrahydropyranyl ether was neccessary to attain selective oxidation of the secondary alcohol at C_5 in **40** to give **41**. Flash vacuum thermolysis (FVT) was carried out with the oxidized compound **41**, rather than with the alcohol **40** for reason of better volatility of the former compound. This order of reactions is a nice example of choosing the right moment for FVT in a synthetic sequence. In the final step reduction of the triple bond using a Lindlar catalyst afforded the desired precursor **44** in a high overall yield (45%, based on **20**).

The preparation of **37** could be accomplished by reduction of the epoxy and ester group in one step by prolonged treatment of compound **36** with lithium aluminum hydride. An attempt to selectively protect the primary hydroxyl group of compound **37** did not meet with succes. It was found, however, that the sequence of reduction-protection-reduction is very practical. A drawback is the introduction of an extra stereogenic center in compound **39** via the tetrahydropyranyl ether unit, which makes the characterization

of the products rather troublesome because of the diastereoisomeric mixtures obtained. For that reason product **41** was deprotected to give diol **42** which could be characterized by spectroscopic means without any problem.

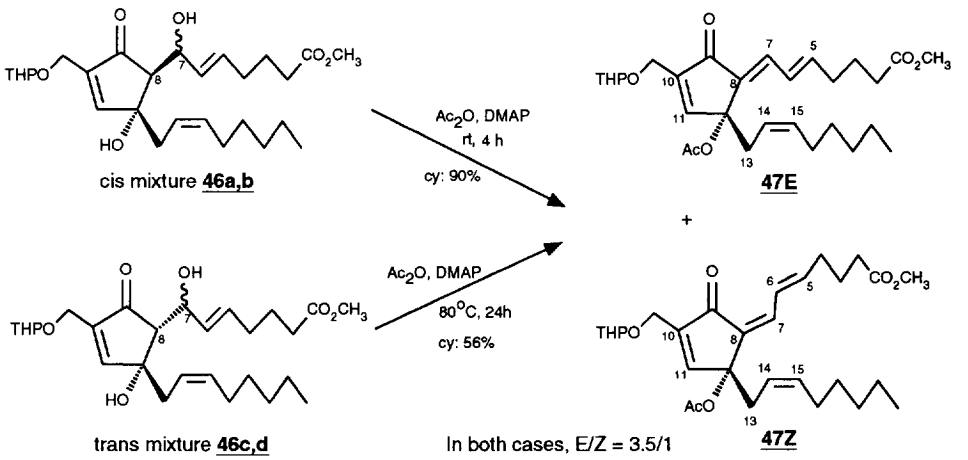
The introduction of the second side chain in precursor **44** was accomplished as depicted in Scheme 12. Aldol condensation of the lithium enolate derived from precursor **44** (by treatment with 3 equiv. of lithium diisopropylamide) with unsaturated aldehyde[5b,14b] **45** (2 equiv.) in tetrahydrofuran at -78°C for 2 hrs smoothly furnished a mixture of diastereoisomers **46** in 90% yield (based on consumed **44**). This

Scheme 12



mixture, in principle, contains 8 diastereoisomers due to the stereogenic centers at C_7, C_8 and the tetrahydropyran unit. Column chromatography resulted in the partial isolation of compounds **46a,b** (*cis*-configuration of the side chains) and compounds **46c,d** (*trans*-configuration of the side chains) with unspecified stereochemistry at C_7 and the tetrahydropyranyl unit in both cases. The attempted elimination of the β-hydroxyl groups at C_7 in **46** by using either 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or mesylation with subsequent base treatment did not produce the desired products. Satisfactory results were obtained however, by a base-induced elimination of the corresponding acetates of **46** (Scheme 13).

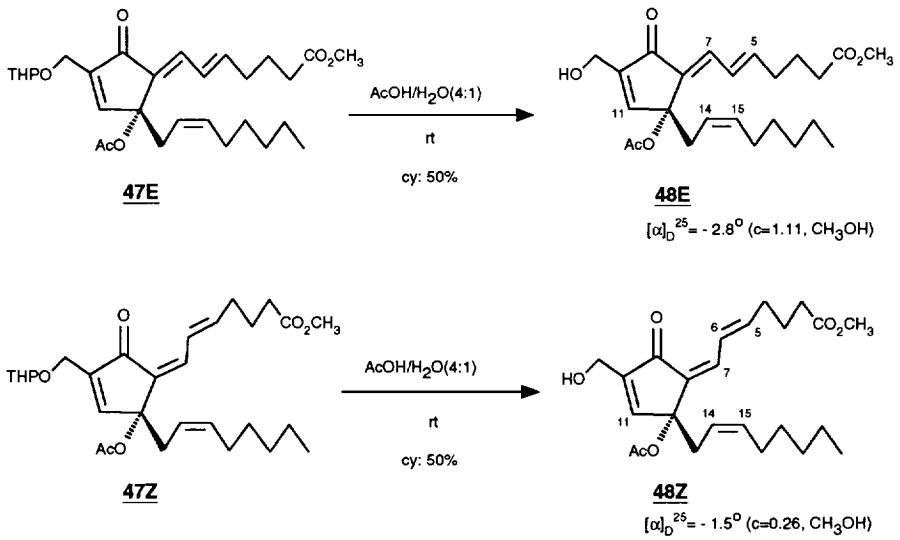
Scheme 13



Treatment of the mixture of **46a,b** with acetic anhydride at room temperature in the presence of 4-dimethylaminopyridine (DMAP), smoothly gave the desired products **47E** and **47Z** in more than 90% yield and in a 3.5:1 ratio, which could be readily separated by chromatography. When the same treatment was carried out with the mixture of **46c,d**, acetate intermediates did not eliminate at all at room temperature. However, complete acetate elimination was accomplished upon heating the mixture at reflux in benzene for 24 h, to give the respective geometrical isomers **47E** and **47Z** as a mixture again in a ratio

of 3.5:1, but now in a moderate yield of 56%. The slower reaction rate observed for the elimination in the acetates of **46c,d** may be due either to the decreased accessibility of proton H_8 in these *trans*-α,β-dialkylated cyclopentenones as compared with their *cis*-isomers **46a,b** or to an increase of the Van der Waals interactions between the two *trans*-alkyl chains which, upon deprotonation, are forced from a *trans*-configuration into a '*gauche*'-configuration. Deprotonation at C_8 in both the acetates of **46a,b** and **46c,d** brings about the same enolate mixture which then rapidly eliminates to form the observed alkene mixture. The finding that the alkene ratio is the same for both mixtures **46a,b** and **46c,d** indicates that product formation is thermodynamically driven. In the final step, deprotection of both **47E** and **47Z** was carried out using acetic acid in water (80%) to give **48E** and **48Z** in 50% yield, respectively (Scheme 14).

Scheme 14



47E **48E**

$[\alpha]_D^{25}$= - 2.8° (c=1.11, CH_3OH)

47Z **48Z**

$[\alpha]_D^{25}$= - 1.5° (c=0.26, CH_3OH)

Both **48E** and **48Z** are not stable when stored at room temperature. This instability may be the reason for the moderate yield obtained during the deprotection step. The final products **48E** and **48Z** showed an optical rotation of $[\alpha]_D^{25}$= -2.8° (c=1.11, CH_3OH) and -1.2° (c=0.26, CH_3OH) and had NMR and IR spectra which showed high resemblance to those of clavulone-type compounds[3,5]. No attempt has been made to establish the enantiopurities of **48E** and **48Z**. Since cyclopentenone **44** was been obtained from enantiopure cyclic ester (+)-**20** applying essentially the same approach as used for the synthesis of (-)-**13**, in which the enantiopurity of (-)-**13** has unequivocally been established, compound **44** should be also enantiopure. As no racemization at the chiral center of C_4 in **44** is conceivable during the subsequent condensation and elimination reactions, analogues **48E** and **48Z** should also be enantiopure. The remarkably low optical rotations observed for **48E** and **48Z** are not deviating from the optical rotations observed for other clavulone-type compounds, some of them also have low values[3a,5a,b,14e]. The assumed *trans*-configuration of the C_5-C_6 double bond and the *cis*-configuration of the C_{14}-C_{15} double bond in both compounds **48E** and **48Z** were confirmed by the coupling constants observed for the olefinic protons, $J_{5,6}$=15.0 Hz and 15.3 Hz, and $J_{14,15}$=10.9 Hz and 10.8 Hz, respectively (Table 1). The *Z* configuration of the C_7-C_8 double bond in **48Z** was proven by the observation of a relative low-field shift for H_6 (δ 7.58) in **48Z** as compared with H_6 (δ 6.54) in **48E**. In a similar way, the *E* configuration of the C_7-C_8 double bond

Table 1. Selected ^{1}H-NMR data (400 MHz) of **48E** and **48Z**

	H_5	H_6	H_7	H_{11}	H_{14} and H_{15}
48E	δ 6.23(dt, $J_{4,5}$=7.0, $J_{5,6}$=15.0 Hz)	δ 6.54(dd, $J_{5,6}$=15.0, $J_{6,7}$=11.9 Hz)	δ 6.92 (d, $J_{6,7}$=11.8 Hz)	δ 7.29(s)	δ 5.50 and 5.17 ($J_{14,15}$=10.9 Hz)
48Z	δ 6.13(dt, $J_{4,5}$=7.0, $J_{5,6}$=15.3 Hz)	δ 7.58(dd, $J_{5,6}$=15.4, $J_{6,7}$=11.4 Hz)	δ 6.55 (d, $J_{6,7}$=11.3 Hz)	δ 7.31(s)	δ 5.51 and 5.21 ($J_{14,15}$=10.8 Hz)

in **48E** could be derived from the relative low-field shift observed for H_7 (δ 6.92) in **48E** as compared with H_7 (δ 6.55) in **48Z**. The deshielding observed for proton H_6 in **48Z** and H_7 in **48E** are the result of the anisotropic effect of the cyclopentenone carbonyl group.

In this paper it has been shown that the stereo- and enantioselective synthesis of clavulones and analogues thereof can indeed be realized starting from endo-tricyclo[5.2.1.$0^{2,6}$]decadienone 2-carboxylic compound **20**. Further studies to extend this approach to the synthesis of halovulones are in progress[23,24].

Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AM-400 spectrophotometer, using TMS as an internal standard. For mass spectra a double focussing VG 7070E mass spectrometer was used. Capillary GC analyses were performed using a Hewlett-Packard 5890A gas chromatograph, containing a cross-linked methyl silicone column (25m). Flash chromatography was carried out at a pressure of ca. 1.5 bar, a column length of 15-25 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60H. Elemental analyses were performed on a Carlo Erba Instruments CHNS-O 1108 Elemental analyzer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Flash Vacuum Thermolyses was carried out using the FVT apparatus as developed at the Organic Laboratory of the Nijmegen University. All solvents used were dried and distilled according to standard procedures.

(+)-(1R,2R,6R,7S)-Endo-*tricyclo[5.2.1.0^{2,6}]-dec-4,8-en-3-one* **14**

Method 1: Barton's radical decarboxylation[17]

A solution of carboxylic acid (-)**21** (190 mg, 1 mmol, $[\alpha]_D^{22}$= -83°, c=0.66, CH_3OH) in benzene (5 ml) was treated with oxalyl chloride (0.3 ml) and a drop of dimethylformamide with stirring at room temp. After stirring for 2 hrs with protection from moisture, the solvent and excess oxalyl chloride was evaporated and the residual acid chloride was used as such.

A solution of acid chloride in benzene (5 ml) was added dropwise (15 min.) to a dried, stirred suspension of N-hydroxypyridin-2-thione sodium salt (180 mg, 1.2 mmol) in refluxing benzene (10 ml) containing t-butyl mercaptan while irradiating with a 250 W tungsten lamp in an inert atmosphere. After completion of the addition, the reaction mixture was cooled to room temp. and evaporated to dryness. The crude product was purified by flash chromatography over silica gel (n-hexane/ethyl acetate = 95/5) to give (+)-**14**

(90 mg, 62%) as a white crystalline material, $[\alpha]_D^{25}$= +139°, (c=0.95, CH_3OH).
(+)-**14**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, $J_{4,5}$=5.7 Hz, $J_{5,6}$=2.6 Hz, 1H, H_5), 5.96 (d, $J_{4,5}$=5.7 Hz, 1H, H_4), 5.94 A of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.9 Hz, 1H, H_8 or H_9), 5.78 B of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=3.0 Hz, 1H, H_8 or H_9), 3.42, 3.22 and 2.97 (3 x brs, 3H, H_1, H_6 and H_7), 2.80 (dd, $J_{1,2}$= $J_{2,6}$=5.1 Hz, 1H, H_2), 1.74 and 1.63 AB x 2 (2 x d, $J_{10a,10s}$=8.4 Hz, 2H, H_{10a} and H_{10s}). GCEI/MS: m/e (%) 146 (84, M^+), 118 (33, M^+-CO), 81 (13, M^++1-C_5H_6), 66 (100, $C_5H_6^+$).

Method 2: thermal decarboxylation
A solution of (-)**21** (190 mg, 1 mmol, $[\alpha]_D^{22}$= -83°, c=0.66, CH_3OH) in DMF (10 ml) was stirred at 100-110 °C for 24 hrs in a N_2 atmosphere. The reaction mixture was concentrated *in vacuo* and further purified by flash chromatography (n-hexane/ethyl acetate = 95/5) to give **14** (115 mg, 78%) as a white crystalline material, $[\alpha]_D^{25}$= +138.5°, (c=0.41, CH_3OH).

(+)-(1R,2S,4S,5S,6R,7S)-exo-*4,5-Epoxy-endo-tricyclo[5.2.1.0^{2,6}]-dec-8-en-3-one* **15**
Hydrogen peroxide (35%, 3ml) and an aqueous solution of sodium hydroxide (0.2 N, 4ml) were added to a solution of (+)-**14** (970 mg, 6.6 mmol, $[\alpha]_D$= +139°, c=0.95, CH_3OH, ee= 99%) in CH_2Cl_2/CH_3OH (1:1, 20 ml) with vigorous stirring at room temp. Stirring was continued for 30 min. The mixture was poured into dichloromethane (100ml) and washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was chromatographed (n-hexane/ethyl acetate = 95/5) to give a sticky solid **15** (1.03g, 95%).
15: $[\alpha]_D^{25}$= +189.2° (c=0.46, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.09 (dd, $J_{8,9}$=5.7 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.5 Hz, 1H, H_8 or H_9), 6.03 (dd, $J_{8,9}$=5.7 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.8 Hz, 1H, H_8 or H_9), 3.58 (t, $J_{4,5}$=1.9 Hz, 1H, H_4), 3.20-3.25 (m, 2H, H_2 and H_5), 3.08-3.11 (m, 2H, H_1 and H_7), 2.74-2.79 (m, 1H, H_6), 1.62 A of AB (dt, $J_{10a,10s}$=5.6 Hz, 1H, one of H_{10}), 1.46 B of AB (d, $J_{10a,10s}$=5.6 Hz, 1H, one of H_{10}). IR (CH_2Cl_2): ν 3100-2820 (C-H), 1735(C=O), 1120, 1090 cm^{-1}. EI/MS: m/e 162(M^+), 97(M+1-C_5H_6). Found: C 73.91, H 6.13 [calc. for $C_{10}H_{10}O_2$: C 73.05, H 6.21].

(+)-(1R,2S,3S,4S,5S,6R,7S)-exo-*3-(Oct-2-ynyl)*-exo-*4,5-epoxy-endo-tricyclo[5.2.1.0^{2,6}]dec-8-en*-endo-*3-ol*
25
Zinc powder (7.5 g, 0.12 mol) was added rapidly to a stirred, heated solution (120 °C) of copper(II) acetate (0.75 g, 4 mmol) in acetic acid (37 ml). The mixture was stirred for an additional 1 min. and then filtered while hot. The powder was washed several times with ether, then heated under reduced pressure (oil pump, 120°C) for one hr. After cooling to room temp., 50 ml of THF and 1-bromo-2-octyne (2.84 g, 15 mmol) was added and the mixture refluxed for 2 hrs in a N_2 atmosphere. After cooling to room temp., a solution of (+)-**15** (540 mg, 3.3 mmol) in THF (10 ml) was added. The stirring was continued overnight. The reaction mixture was poured into saturated NH_4Cl solution (50 ml) and extracted with ether (4 × 50 ml), washed with water, brine, dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash chromatography (n-hexane/ethyl acetate = 97/3) to give **25** (820 mg, 90 %) as a light yellow oil.
25: $[\alpha]_D^{25}$= +102.3° (c=0.83, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.27 and 6.05 AB (2 x dd, 2H, H_8 and H_9), 3.19-3.15 (m, 2H, H_4 and H_5), 2.95-2.90 (m, 2H, H_1 and H_7), 2.80-2.85 (m, 1H, H_2), 2.40-2.62 (m, 3H, H_6 and H_{10}), 2.30 (s, 1H, OH), 2.17-2.19 (m, 2H, H_{11}), 1.40-1.65 and 1.29-1.35 [2 x m, 8H,

-$(CH_2)_4$-], 0.90 (t, J=7.2 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3540 (free OH), 3100-2820 (C-H) cm^{-1}. EI/MS: m/e(%) 272 (0.6, M^+), 206 (6, M^+-C_5H_6), 189 (3, M^++1-C_5H_6-H_2O), 67 (100, $C_5H_6^+$+1). EI/HRMS m/e 272.1777 [calc. for $C_{18}H_{24}O_2(M^+)$: 272.1776].

(+)-(1*R*,2*S*,3*R*,5*R*,6*R*,7*S*)-exo-3-(Oct-2-ynyl)-endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-endo-5-exo-diol **27**

Lithium aluminum hydride (500 mg) was suspended in fresh distilled THF (50 ml) with stirring at room temp. Stirring was continued for 30 min. then the mixture was allowed to settle overnight. A clear solution of lithium aluminum hydride (40 ml) was now added to a solution of epoxide (+)-**25** (390 mg, 1.43 mmol) in THF (20 ml) with stirring at room temp. under a N_2-atmosphere. The stirring was continued for 3 days. Reaction was stopped by carefully adding ethyl acetate (10 ml) and saturated NH_4Cl aq. (0.5 ml). Stirring was continued for 30 min., Na_2SO_4(30 g) was added and the mixture stirred for another 30 min. The solid was filtered off and washed with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (n-hexane/ethyl acetate = 8/2) provided (+)-**27** (325 mg, 83%) as a colorless oil.

27: $[\alpha]_D^{25}$= +43.5°(c=0.95, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.29 A of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.9 Hz, 1H, H_8 or H_9), 6.03 B of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=3.0 Hz, 1H, H_8 or H_9), 3.78 (d, $J_{4,5}$=6.3 Hz, 1H, H_5), 2.90 and 2.96(2 x brs, 2H, H_1 and H_7), 2.83 (m, 1H, H_2), 2.66 (m, 1H, H_6), 2.62 and 2.54 AB system (2 x dt, $J_{11a,b}$=13.6 Hz, 2H, H_{11}), 2.19(m, 2H, H_{14}), 2.05 (brs, 1H, OH), 1.90 A of AB (dd, $J_{a,b}$=14.1 Hz, $J_{4,5}$=6.3 Hz, 1H, one of H_4), 1.72 B of AB (d, J=14.1 Hz, 1H, one of H_4), 1.63 (brs, 1H, OH), 1.25-1.55 (m, 8H, H_{10} and -$(CH_2)_3$-), 0.90(t, J=7.2 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3590 (free OH), 3100-2820 (C-H) cm^{-1}. CI/MS: m/e(%) 275 (0.5, M^++1), 257 (9, M^++1-H_2O), 239 (8, M^++1-2H_2O), 208 (4, M^+-C_5H_6), 99 (100,), 66 (29, $C_5H_6^+$). CI/HRMS m/e 274.1929 [calc. for $C_{18}H_{26}O_2(M^+)$: 274.1933].

(+)-(1*R*,3*R*)-1-(Oct-2-ynyl)-cyclopent-4-en-1,3-diol **28**

Flash vacuum thermolysis of (+)-**27** (400 mg, 1.46 mmol) [sample temp: 120°C; oven temp: 550°C; cold trap temp: -78°C; pressure: 3×10^{-2} mbar] and purification by flash chromatography (n-hexane/ethyl acetate = 3/1) provided pure compound **28** (220 mg, 72%).

28: $[\alpha]_D^{25}$= +31.8° (c=0.69, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.98 (dd, $J_{4,5}$=5.6 Hz, $J_{3,4}$=2.2 Hz, 1H, H_4), 5.89 (d, $J_{4,5}$=5.6 Hz, 1H, H_5), 4.96 (d x m, $J_{2a,3}$=7.2 Hz, 1H, H_3), 2.60 AB (dd, 2H, H_6), 2.33 A of AB (dd, $J_{a,b}$=14.4 Hz, $J_{2a,3}$=7.2 Hz, 1H, one of H_2), 2.14-2.20 (m, 2H, H_9), 1.93 B of AB (dd, $J_{a,b}$=14.4 Hz, $J_{2b,3}$=2.8 Hz, 1H, one of H_2), 1.52-1.25 [m, 8H, 2 x OH and -$(CH_2)_3$-], 0.90 (t, J=7.2 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3580 (free OH), 3600-3100(H-bonded OH), 3100-2820 (C-H), 1055 cm^{-1}. CI/MS: m/e(%) 208 (0.2, M^+), 191 (26, M^++1-H_2O), 173 (21, M^++1-2×H_2O), 99 (100, M^+-chain). CI/HRMS m/e 208.1463 [calc. for $C_{13}H_{20}O_2(M^+)$: 208.1463].

(-)-(4*R*)-4-Hydroxy-4-(oct-2-ynyl)-cyclopent-2-enone **29**

A solution of (+)-**28** (180 mg, 0.87 mmol) in dichloromethane (18 ml) was treated with pyridinium chlorochromate (470 mg, 2.18 mmol) in the presence of 3Å molecular sieves (320 mg) at room temp. for 4 hrs. The solid was filtered off over silica gel (4 g) and washed with hexane-ethyl acetate (1:1). The combined organic layers were evaporated, and the residue chromatographed (n-hexane/ethyl acetate = 8/2) to give (-)-**29** (160 mg, 90%) as a colorless oil.

29: $[\alpha]_D^{25}$= -137.1° (c=0.89, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47 (d, $J_{2,3}$=5.6 Hz, 1H, H_3), 6.17 (d, J=5.6 Hz, 1H, H_2), 2.62 and 2.51 AB x 2 (2 x d, $J_{a,b}$=18.3 Hz, 2H, H_5), 2.63 (m, 2H, H_6), 2.15-2.19 (m, 2H, H_9), 1.65 (brs, 1H, OH), 1.36-1.47 [m, 6H, -$(CH_2)_3$-], 0.90 (t, J=7.2 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3600-3100 (OH), 3100-2820 (C-H), 1720 (C=O) cm^{-1}. CI/MS: m/e(%) 207 (100, M^++1), 189 (35, M^++1-H_2O), 97 (89, M^+-chain). CI/HRMS m/e 206.1304 [calc. for $C_{13}H_{18}O_2(M^+)$: 206.1307].

(-)-(4R)-4-Hydroxy-4-(oct-2-enyl)-cyclopent-2-enone **13**

Hydrogenation of (-)-**29** was carried out at room temp. and 1 bar of hydrogen pressure. The reaction mixture contained (-)-**29** (100 mg) and Lindlar catalyst (5 mg, from Aldrich) in toluene (10 ml). Reaction progress was followed by measuring the amount of consumed hydrogen and analyzing the reaction mixture by gas chromatography. After filtering off the catalyst and evaporation of the solvents, a mixture of desired product **13** (84%) and by-product **30** (9%) was obtained. Products were separated by careful chromatography (n-hexane/ethyl acetate = 8/2).

13: $[\alpha]_D^{25}$= -84.0°(c=0.31, $CHCl_3$)(lit.[14b] $[\alpha]_D$= -54.1°, c=1.52, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42(d, $J_{2,3}$=5.6 Hz, 1H, H_3), 6.14 (d, J=5.6 Hz, 1H, H_2), 5.67 and 5.38 (2 x m, 2H, H_7 and H_8), 2.56 A of AB (d, $J_{a,b}$=18.4 Hz, 1H, H_{5a}), 2.45 B of AB (d, J=18.4 Hz, 1H, H_{5b}), 2.40-2.60 (m, 2H, H_6), 2.20 (brs, 1H, OH), 2.02-2.08 (m, 2H, H_9), 1.25-1.40 [m, 6H, -$(CH_2)_3$-], 0.89 (t, J=6.8 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3570 (free OH), 3600-3100(OH), 3010-2820 (C-H, sat.), 1715(C=O), 1045 cm^{-1}. CI/MS: m/e(%) 209 (64, M^++1), 191 (50, M^++1-H_2O), 98 (100, M^++1-chain). CI/HRMS m/e 190.1355 [calc.for $C_{13}H_{20}O_2(M^+$-$H_2O)$: 190.1358].

(4R)-3-Hydroxy-3-(oct-2-enyl)-cyclopentanone **30**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.69 and 5.45 (2 x m, 2H, H_7 and H_8), 2.45-2.59 and 2.24-2.33 (m, 6H, $H_{2,5,6}$), 1.98-2.11 (m, 4H, H_9 and H_4), 1.71 (brs, 1H, OH), 1.25-1.39 [m, 6H, -$(CH_2)_3$-], 0.89 (t, J=6.8 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3570 (free OH), 3600-3100(OH), 3010-2820 (C-H, sat.), 1735(C=O) cm^{-1}. CI/MS: m/e(%) 211 (95, M^++1), 193 (100, M^++1-H_2O), 112 [38, (octenyl)$^+$+1], 99 (82, M^+-chain). CI/HRMS m/e 210.1619 [calc.for $C_{13}H_{22}O_2(M^+)$: 210.1620].

(-)-(1R,4S)-(1,4-Dihydroxy-cyclopent-2-enyl)-acetic acid t-butyl ester **32**

A solution of t-butyl acetate (3.5 g, 30 mmol) in tetrahydrofuran (5 ml) was added to a solution of lithium diisopropylamide (24 mmol, prepared from 30 mmol of diisopropylamine and 24 mmol of n-butyllithium) in freshly distilled tetrahydrofuran (15 ml) with stirring and cooling (-78 °C). After stirring for 30 min. at -78 °C, a solution of enone alcohol **31**[19] (980 mg, 10 mmol, ee= 51%) in tetrahydrofuran (10 ml) was added dropwise (30 min.). Stirring was continued at -78°C for another 15 min. then the reaction mixture was poured into ice-water (ca. 25 ml), extracted with ethyl acetate (3x), washed with NH_4Cl aq. and saturated NaCl aq., dried (Na_2SO_4) and concentrated *in vacuo* to give a crude oil. Flash chromatography (n-hexane/ethyl acetate = 1/1) gave pure (-)-**32** (1.51 g, 70.6%) as a colorless oil, $[\alpha]_D^{22}$= 27.7° (c=1.39, $CHCl_3$). After storing in the refrigerator for 2 weeks, it slowly crystallized. Recrystallization from diisopropyl ether until constant optical rotation (after more than eight times) gave nice crystals with $[\alpha]_D^{25}$= -56.6° (c=1.32, $CHCl_3$) (Lit.[14b] $[\alpha]_D$= -45.9°,c=1.12, $CHCl_3$) and m.p. 69.5-71.0 °C.

32: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.98 A of AB (dd, $J_{2',3'}$=5.6 Hz, $J_{3',4'}$=2.0 Hz, 1H, $H_{3'}$), 5.94 B of AB (d, $J_{2',3'}$=5.6 Hz, 1H, $H_{2'}$), 4.66 (m, 1H, $H_{4'}$), 4.20 (brs, 1H, OH), 2.54 and 2.49 AB (2 x d, $J_{a,b}$=15.8 Hz,

2H, H_2), 2.40 (brs, 1H, OH), 2.40 A of AB (dd, $J_{a,b}$=14.2 Hz, $J_{4',5'a}$=7.0 Hz, 1H, $H_{5'a}$), 1.88 B of AB (dd, $J_{a,b}$=14.2 Hz, $J_{4',5'b}$=3.4 Hz, 1H, $H_{5'b}$), 1.47 [s, 9H, $C(CH_3)_3$]. IR (CH_2Cl_2): ν 3580 (free OH), 3600-3100(H-bonded OH), 3010-2820 (C-H, sat.), 1720(C=O) cm^{-1}. CI/MS: m/e(%) 215 (24, M^++1), 197 (26, M^++1-H_2O), 159 [25, M^++2-$C(CH_3)_3$], 141 (100, -H_2O), 99 [30, M^+-$CH_2COOC(CH_3)_3$], 57 [53, $C(CH_3)_3$]. CI/HRMS m/e 214.1205 [calc.for $C_{11}H_{18}O_4(M^+)$: 214.1205].

(-)-(*1R,2R,3R,4R,6R,7S*)-exo-*3,4-Epoxy*-endo-*tricyclo[5.2.1.0^{2,6}]deca-8-ene-2-carboxylic acid ethyl ester* **35**

To a solution of (+)-**20** (3 g, 14 mmol, $[\alpha]_D^{25}$= +107.8° CH_3OH, ee ≥ 98%) in dichloromethane/methanol (1:1, 30 ml) was added a mixture of hydrogen peroxide (35%, 7.5 ml) and aq. sodium hydroxide (0.2 N, 9 ml) with vigorous stirring at room temp. Stirring was continued for 30 min. The mixture was then poured into dichloromethane (100 ml), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give almost pure **35** (3.3 g, 100 %) as a white solid. An analytically pure sample was obtained by recrystallization.

35: m.p.: 110-112 °C (diisopropyl ether). $[\alpha]_D^{25}$= -27.9° (c= 2.07, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.22 A of AB (dd, $J_{8,9}$=5.7 Hz, $J_{1,9}$ resp. $J_{7,8}$=3.1 Hz, 1H, H_8 or H_9), 6.16 B of AB (dd, $J_{8,9}$=5.5 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.8 Hz, 1H, H_8 or H_9), 4.29 (m, 2H, $COOCH_2CH_3$), 3.84 (t, J=2.0 Hz, 1H, H_4), 3.33(brs, 1H, H_1 or H_7), 3.30-3.28 (m, 2H, H_3 and H_1 or H_7), 3.26 (dd, J=4.8 Hz, J=1.8, 1H, H_6), 1.81 and 1.59 AB (2 x d, $J_{10a,s}$=9.0 Hz, 2H, H_{10}), 1.35 (t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 1700 and 1720(C=O). EI/MS: m/e(%) 234 (1, M^+), 205 (2, M^+-CH_2CH_3), 189 (7, M^+-OCH_2CH_3), 169 (81, M^++1-C_5H_6), 66 (100, $C_5H_6^+$). EI/HRMS m/e 234.0892 [calc.for $C_{13}H_{14}O_4(M^+)$: 234.0892]. Found C 66.53 % H 6.01 [calc. for $C_{13}H_{14}O_4$: C 66.66 % H 6.02 %].

(-)-*(1R,2R,3R,4R,5R,6R,7S)-3,4-Epoxy-5-hydroxy-5-(oct-2-ynyl)*-endo-*tricyclo[5.2.1.0^{2,6}]deca-8-ene-2-carboxylic acid ethyl ester* **36**

Zinc powder (9.5 g, 0.15 mol) was rapidly added to a stirred, heated solution (120 °C) of copper(II) acetate (0.95 g, 5 mmol) in acetic acid (47 ml). The mixture was stirred for an additional 1 min. and then filtered while hot. The powder was washed several times with ether and then heated under reduced pressure (oil pump, 120 °C) for one hr. After cooling to room temp., 50 ml of tetrahydrofuran and 1-bromo-2-octyne (4 g, 21 mmol) were added and the mixture refluxed for 2 hrs under a N_2 atmosphere. After cooling to room temp., a solution of (-)-**35** (1 g, 4.2 mmol) in THF (10ml) was added. The stirring was continued overnight. The reaction mixture was poured into saturated aq. NH_4Cl (50 ml) and extracted with ether (4 × 50 ml), washed with water, brine, dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash chromatography (n-hexane/ethyl acetate = 97/3) to give **36** (1.25 g, 86 %) as a light yellow oil.

36: $[\alpha]_D^{25}$= -23.1° (c= 2.11, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.42 A of AB (dd, $J_{8,9}$=5.5 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.8 Hz, 1H, H_8 or H_9), 6.13 B of AB (dd, $J_{8,9}$=5.5 Hz, $J_{1,9}$ resp. $J_{7,8}$=3.1 Hz, 1H, H_8 or H_9), 4.22 (q, J=7.1 Hz, 2H, $COOCH_2CH_3$), 3.42 and 3.21 (2 x d, $J_{3,4}$=2.1 Hz, 2H, H_3 and H_4), 3.11 (brs, 1H, H_1 or H_7), 3.04 (d, $J_{6,7}$=4.0 Hz, 1H, H_6), 3.00 (brs, 1H, H_1 or H_7), 2.58 A of AB (dt, $J_{a,b}$=8.4 Hz, J=2.3 Hz, 1H, H_{10s}), 2.45 B of AB (dt, $J_{a,b}$=8.4 Hz, J=2.3 Hz, 1H, H_{10a}), 2.38 (s, 1H, OH), 2.18 (m, 2H, H_{11}), 1.58-1.26 (m, 8H, -$(CH_2)_4$-), 0.90 (t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3540 (free OH), 3010-2820 (C-H, sat.),

1725 (C=O) cm^{-1}. CI/MS: m/e(%) 345 (5, M^++1), 327 (4,-H_2O), 278 (6, M^+-C_5H_6), 235 (26, M^++1-chain), 169 (100, M^++1-chain-C_5H_6), 66 (46, $C_5H_6^+$+1). EI/HRMS m/e 345.2062 [calc. for $C_{21}H_{29}O_4(M^+$+1): 345.2066].

(1R,2R,3S,5S,6R,7S)-2-Hydroxymethyl-5-(oct-2-ynyl)-endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,5-diol **37**

Lithium aluminum hydride (500 mg) was added to freshly distilled tetrahydrofuran (50 ml) with stirring at room temp. Stirring was continued for 30 min. and then the mixture was stored overnight. A clear solution of lithium aluminum hydride (40 ml) was added to a solution of epoxide **36** (400 mg, 1.16 mmol) in tetrahydrofuran (20 ml) with stirring at room temp. and under a N_2-atmosphere. Stirring was continued for 4 days. The reaction was stopped by carefully adding ethyl acetate (10 ml) and saturated NH_4Cl aq. (0.5ml). Stirring was continued for 30 min. at room temp., then Na_2SO_4 (30 g) was added and the mixture stirred for another 30 min. Solid was filtered off and washed with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (n-hexane/ethyl acetate = 8/2) provided **37** (325 mg, 80 %) as a colorless oil.

37: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.38 A of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.9 Hz, 1H, H_8 or H_9), 6.15 B of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=3.1 Hz, 1H, H_8 or H_9), 4.09 and 3.69 AB (2 x d, $J_{a,b}$=11.0 Hz, 1H, CH_2OH), 3.96 (dd, $J_{3,4a}$=7.0 Hz, $J_{3,4b}$=2.5 Hz, 1H, H_3), 2.96 and 2.88(2 x brs, 2H, H_1 and H_7), 2.57 AB (2 x dt, 2H, H_{10}), 2.74 and 2.45 (2 x OH), 2.30 (m, 1H, H_2), 2.18 (m, 2H, H_{11}), 2.10 A of AB (dd, $J_{a,b}$=13.6 Hz, $J_{3,4a}$=7.0 Hz, 1H, one of H_4), 1.84 B of AB (dd, $J_{a,b}$=13.6 Hz, $J_{3,4b}$=2.5 Hz, 1H, one of H_4), 1.64 (brs, 1H, OH), 1.60-1.29 [m, 8H, -$(CH_2)_3$-], 0.90 (t, J=7.1 Hz, CH_3). IR (CH_2Cl_2): ν 3600, 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H) cm^{-1}. CI/MS: m/e(%) 305 (6, M^++1), 287 (11, M^++1-H_2O), 269 (28, M^++1-2xH_2O), 195 (89, M^+-chain), 129 (100, M^+-C_5H_6-chain), 66 (35, $C_5H_6^+$). CI/HRMS m/e 305.2127 [calc. for $C_{19}H_{29}O_3(M^+$+1): 305.2117].

(-)-(1S,2R,3R,4R,5R,6S,7R)-4,5-Epoxy-6-hydroxymethyl-3-(oct-2-ynyl)-endo-*tricyclo[5.2.1.$0^{2,6}$]-dec-8-en-3-ol* **38**

Lithium aluminum hydride (1 g) was added to freshly distilled tetrahydrofuran (100 ml) with stirring at room temp. Stirring was continued for 30 min. and then the mixture stored overnight. A clear solution of lithium aluminum hydride (60 ml) was added to a solution of epoxide (-)-**36** (1.5 g, 4.3 mmol) in tetrahydrofuran (20 ml) with stirring at room temp. and under a N_2-atmosphere. The stirring was continued for 2 hrs. Reaction was stopped by carefully adding ethyl acetate (10 ml) and saturated NH_4Cl aq. (1 ml). Stirring was continued for 30 min. at room temp., Na_2SO_4 (60g) was added and the mixture stirred for another 30 min. Solid was filtered off and washed with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (n-hexane/ethyl acetate = 7/3) provided **38** (1.24 g, 93 %) as a colorless oil.

38: $[\alpha]_D^{25}$= -42.2° (c=0.95, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.35 A of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.8 Hz, 1H, H_8 or H_9), 6.12 B of AB (dd, $J_{8,9}$=5.6 Hz, $J_{1,9}$ resp. $J_{7,8}$=3.1 Hz, 1H, H_8 or H_9), 3.82 and 3.72 AB (2 x d, $J_{a,b}$=11.0 Hz, 2H, CH_2OH), 3.30 and 3.23 (2 x d, $J_{4,5}$=2.3 Hz, 2H, H_4 and H_5), 2.91 and 2.79(2 x brs, 2H, H_1 and H_7), 2.59 and 2.43 AB (2 x dt, $J_{a,b}$=16.4 Hz, 2H, H_{10}), 2.39 and 2.37 (2 x OH), 2.23 (d, $J_{1,2}$=4.0 Hz, 1H, H_2), 2.18 (m, 2H, H_{11}), 1.51-1.25 (m, 8H, -$(CH_2)_4$-), 0.90(t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3600, 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H) cm^{-1}. CI/MS:

m/e(%) 303 (10, M^++1), 285 (16, M^++1-H_2O), 267 (16, M^++1-2xH_2O), 236 (13, M^+-C_5H_6), 127 (100, M^+-C_5H_6-chain), 66 (69, $C_5H_6^+$). CI/HRMS m/e 303.1958 [calc. for $C_{19}H_{27}O_3$(M^++1): 303.1960].

(1S,2R,3R,4R,5R,6S,7R)-4,5-Epoxy-3-(oct-2-ynyl)-6-(tetrahydro-pyran-2-yloxymethyl)-endo-*tricyclo-[5.2.1.$0^{2,6}$]dec-8-en-3-ol* **39**

A solution of (-)-**38** (4.4 g, 14.5 mmol) in dichloromethane (80 ml) was treated with dihydropyran (4.2 g, 50 mmol) and p-toluenesulfonic acid (10 mg) at room temp. After stirring for 3 hrs, the reaction mixture was poured into dichloromethane (150 ml) and washed with saturated NaCl aq., dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (n-hexane/ethyl acetate = 20/1) gave pure **39** (4.0 g, 90 %) as colorless oil (diastereoisomeric mixture).

39: ^{1}H-NMR (400 MHz, $CDCl_3$): (diastereoisomeric mixture due to the presence of THP group) δ 6.33 and 6.15 AB (dd, 2H, H_8 and H_9), 4.67, 4.09, 3.90, 3.66, 3.53 and 3.24 (m, 7H), 3.08, 3.01 and 2.86 (3 x brs, 2H, H_1 and H_7), 2.57 and 2.40 AB (2 x m, 2H, H_{10}), 2.31 (2 x s, 1H, OH), 2.00 and 1.96 (2 x d, 1H, H_2), 2.17 (m, 2H, H_{11}), 1.90-1.20 (m, 13H), 0.90 (t, J=7.1 Hz, CH_3). IR (CH_2Cl_2): ν 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H) cm^{-1}. CI/MS: m/e(%) 387 (0.5, M^++1), 303 (1, M^++1-THP), 285 (2, -H_2O), 85 (100, $C_5H_9O^+$), 66 (9, $C_5H_6^+$). CI/HRMS m/e 387.2534 [calc. for $C_{24}H_{35}O_4$(M^++1): 387.2535].

(1R,2R,3S,5S,6R,7S)-5-(Oct-2-ynyl)-2-(tetrahydro-pyran-2-yloxymethyl)-endo-*tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,5-cis-diol* **40**

Lithium aluminum hydride (1 g) was added to freshly distilled tetrahydrofuran (100 ml) with stirring at room temp. Stirring was continued for 30 min. then kept overnight. A clear solution of lithium aluminum hydride (80 ml) was added to a solution of epoxide **39** (450 mg, 1.2 mmol) in tetrahydrofuran (10 ml) with stirring at room temp. and under a N_2-atmosphere. The stirring was continued for 4 days. The reaction was stopped by carefully adding ethyl acetate (10 ml) and saturated NH_4Cl aq. (1 ml). After stirring for 30 min. Na_2SO_4 (60 g) was added and the mixture stirred for another 30 min. Solid was filtered off and washed with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (n-hexane/ethyl acetate = 7/3) led to recovery of starting material **39** (170 mg) and product **40** (250 mg, 90 % based on consumed **39**) as a colorless oil.

40: ^{1}H-NMR (400 MHz, $CDCl_3$): (diastereoisomeric mixture due to the presence of THP group) δ 6.40 and 6.15 AB (dd, 2H, H_8 and H_9), 4.62, 4.25, 3.84 and 3.51 (m, 6H, -O-CHR-), 2.92 and 2.88 (2 x brs, 2H, H_1 and H_7), 2.70-2.40 AB (m, 2H, H_{10}), 2.34 (2 x d, 1H, H_6), 2.18 (m, 2H, H_{11}), 2.15-1.25 (m, 16H), 0.90 (t, J=7.1 Hz, CH_3), 3.40, 3.12 and 2.15 (3 x brs, 2H, OH). IR (CH_2Cl_2): ν 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H) cm^{-1}. CI/MS: m/e(%) 389 (1, M^++1), 305 (22, M^++1-THP), 287 (9, -H_2O), 269 (14, -H_2O), 195 (85, M^+-THP-chain), 177 (8, -H_2O), 85 (100, $C_5H_9O^+$), 66 (16, $C_5H_6^+$). CI/HRMS m/e 389.2691 [calc. for $C_{24}H_{37}O_4$(M^++1): 389.2692].

(1S,2R,3S,6S,7R)-5-Hydroxy-5-(oct-2-ynyl)-2-(tetrahydro-pyran-2-yloxymethyl)-endo-*tricyclo[5.2.1.$0^{2,6}$]-dec-8-en-3-one* **41**

To a solution of **40** (3 g, 7.7 mmol) in dichloromethane (180 ml) was added a mixture of pyridinium chlorochromate (5.8 g, 27 mmol) in the presence of 3Å molecular sieves (2.4 g) at room temp. The

suspension was stirred overnight at room temp. The solid was filtered off over silica gel and washed with hexane-ethyl acetate (1:1). The combined organic layers were evaporated and the residue chromatographed (n-hexane/ethyl acetate = 8/2) to give product **41** (2.76 g, 92 %) as a colorless oil.

41: ^{1}H-NMR (400 MHz, $CDCl_3$): (diastereoisomeric mixture due to the presence of THP group) δ 6.45 and 6.02 AB (dd, 2H, H_8 and H_9), 4.65, 4.58, 4.35, 3.92, 3.82, 3.64 and 3.52 (m, 5H, -O-CHR-), 3.16-2.77 (m, 3H, H_1,H_6 and H_7), 2.72 and 2.54 (2 x m, 2H, H_{10}), 2.35-2.17 (m, 4H, H_4 and H_{11}), 1.75-1.25 (m, 15H), 0.90 (t, J=7.0 Hz, CH_3), 3.40, 3.12 and 2.15 (3 x brs, 2H, OH). IR (CH_2Cl_2): ν 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H), 1725 (C=O) cm^{-1}. CI/MS: m/e(%) 387 (3, M^++1), 303 (17, M^++1-THP), 237 (54, M^++1-C_5H_6-THP), 193 (37, M^+-THP-chain), 85 (100, $C_5H_9O^+$), 66 (20, $C_5H_6^+$).

(1S,2R,3S,6S,7R,)-5-Hydroxy-5-(oct-2-ynyl)-2-hydroxymethyl-endo-*tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one* **42**

A mixture of **41** (75 mg, 0.2 mmol), fumaronitrile (78 mg, 1 mmol) and ethylaluminum dichloride (1.0 M, 0.5 ml, 0.5 mmol) in 1,2-dichloroethane was stirred at room temp. for 2 hrs. The mixture was poured into 20 ml dichloromethane, washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. Flash chromatography (n-hexane/ethyl acetate = 9/1) gave pure **42** (55 mg, 92%) as colorless oil.

42: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.46 A of AB (dd, $J_{8,9}$=5.5 Hz, $J_{1,9}$ resp. $J_{7,8}$=2.9 Hz, 1H, H_8 or H_9), 6.04 B of AB (dd, $J_{8,9}$=5.5 Hz, $J_{1,9}$ resp. $J_{7,8}$=3.1 Hz, 1H, H_8 or H_9), 3.98 and 3.70 AB (2 x d, $J_{a,b}$=10.7 Hz, 2H, CH_2OH), 3.17 and 2.95 (2 x brs, 2H, H_1 and H_7), 2.74 (d, $J_{6,7}$=4.1 Hz, 1H, H_6), 2.59 and 2.50 AB (2 x dt, $J_{a,b}$=16.4 Hz, 2H, H_{10}), 2.47 (s, 1H, OH), 2.42 (d, J<1 Hz, 2H, H_{11}), 1.70 (s, 1H, OH), 1.60-1.45 (m, 4H, H_{14} and H_{10}), 1.40-1.25 (m, 6H, $H_{15\text{-}17}$), 0.90(t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3600 and 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H), 1720 (C=O) cm^{-1}. CI/MS: m/e(%) 303 (3, M^++1), 285 (11, -H_2O), 267 (5, -H_2O), 237 (94, M^++1-C_5H_6), 66 (100, $C_5H_6^+$). CI/HRMS m/e 303.1958 [calc. for $C_{19}H_{27}O_3$(M^++1): 303.1960].

(4R)-4-hydroxy-4-oct-2-ynyl-2-(tetrahydro-pyran-2-yloxymethyl)-cyclopent-2-enone **43**

Flash vacuum thermolysis of **41** (390 mg, 1 mmol) [sample temp: 150°C; oven temp: 500°C; cold trap temp: -78°C; pressure: 3×10^{-2} mbar] and purification by flash chromatography (hexane/ethyl acetate = 3/1) provided pure compound **43** (260 mg, 82 %) as a colorless oil.

43: ^{1}H-NMR (400 MHz, $CDCl_3$): (diastereoisomeric mixture due to the presence of THP group) δ 7.33 (s, 1H, H_3), 4.67, 4.45, 4.16, 3.85 and 3.52 (5 x m, 5H, -O-CHR-), 2.70 and 2.58 AB (2 x d, $J_{a,b}$=18.4 Hz, 2H, H_5), 2.63 (brs, 2H, H_6), 2.15-2.19 (m, 2H, H_9), 1.90-1.25 (m, 13H), 0.90 (t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3600-3100 (H-bonded OH), 3100-2820 (C-H), 1710 (C=O) cm^{-1}. CI/MS: m/e(%) 321 (2, M^++1), 237 (29, -THP), 85 (100, C_5H_9O). CI/HRMS m/e 321.2067 [calc. for $C_{19}H_{29}O_4$(M^++1)): 321.2066].

(4R)-4-Hydroxy-4-oct-2(cis)-enyl-2-(tetrahydro-pyran-2-yloxymethyl)-cyclopent-2-enone **44**

Hydrogenation was carried out at room temp. and 1 bar of hydrogen pressure using a standard procedure. The reaction mixture contained **43** (100 mg) and Lindlar catalyst (10 mg, from Aldrich) in methanol (10 ml). Reaction progress was followed by measuring the amount of consumed hydrogen and analyzing the product by gas chromatography. After filtering off the catalyst and evaporation of the solvents, desired product **44** (91%) was obtained by careful flash chromatography (n-hexane/ethyl acetate = 8/2).

44: ^{1}H-NMR (400 MHz, $CDCl_3$): (diastereoisomeric mixture due to the presence of THP group) δ 7.30 (s, 1H, H_3), 5.68 and 5.41 AB (2 x dd, 2H, H_7 and H_8), 4.66, 4.44, 4.15, 3.85 and 3.52 (5 x m, 5H, -O-CHR-), 2.65-2.45 (m, 4H, H_5 and H_6), 2.06 (m, 2H, H_9), 1.94-1.25 (m, 13H), 0.89 (t, J=7.0 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3570 (free OH), 3600-3100(H-bonded OH), 3100-2820 (C-H), 1710 (C=O) cm^{-1}. CI/MS: m/e(%) 323 (0.8, M^++1), 239 (11, -THP), 211 (3, -H_2O), 85 (100, $C_5H_9O^+$). CI/HRMS m/e 323.2223 [calc.for $C_{19}H_{31}O_4$(M^++1): 323.2222].

(8S,12R)- and (8R,12R)-5E-4-deacetyl-7,12-dihydroxy-10-(tetrahydropyran-2'-yl-oxymethyl)-7,8-dihydro-clavulone **46**

n-Butyllithium (2.6 ml, 1.6 M, 4.2 mmol) was added to a solution of diisopropylamine in THF (5 ml) with stirring at -30 °C. Stirring was continued for 15 min. After lowering the temp. to -78 °C, a solution of **44** (460 mg, 1.4 mmol) in tetrahydrofuran (5 ml) was added. Stirring was continued at -78 °C for 30 min. and a solution of aldehyde **45**[14b] (420 mg, 4.2 mmol) in tetrahydrofuran (4 ml) was added. The reaction was continued at -78 °C for another 2 hrs. The mixture was then poured into saturated aq. NH_4Cl (20 ml) and extracted with ethyl acetate. The organic layer was washed with aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (n-hexane/ethyl acetate = 3/1) gave two product mixtures **46a,b** (210 mg, 31%) and **46c,d** (215 mg, 32%), and starting material **44** (140 mg, 30%). The yield is 90% based on consumed **44**.

mixture **46a,b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1H, H_{11}), 5.87-5.73 (m, 2H, H_5 and H_6), 5.70-5.60 and 5.52-5.45 (2 x m, 2H, H_{14} and H_{15}), 4.66-4.63, 4.44-4.39, 4.17-4.11, 3.85-3.81, 3.53-3.49, 2.95-2.83 and 2.60-2.44 (7 x m, 9H, H_7, H_8, H_{13}, H_{21}, H_{22} and H_{26}), 3.67 (s, 3H, $COOCH_3$), 2.37-2.32, 2.18-2.11 and 2.05-1.98 (3 x m, 3 x 2H, H_2, H_4 and H_{16}), 1.84-1.20 (m, 16H), 0.88 (t, J=7.0 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H), 1735 and 1710 (C=O) cm^{-1}. CI/MS: m/e(%) 443 (0.2, M^++1-2H_2O), 377 (2, M^++1-THPOH), 359 (3, M^++1-H_2O-THPOH), 341 (1, M^++1-2H_2O-THPOH), 85 (100, $C_5H_9O^+$). CI/HRMS m/e 377.2314 [calc.for $C_{22}H_{33}O_5$(M^++1-THPOH): 377.2328].

mixture **46c,d**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H, H_{11}), 6.05-5.85, 5.75-5.63 (2 x m, 2H, H_5 and H_6), 5.63-5.45 and 5.45-5.35 (2 x m, 2H, H_{14} and H_{15}), 4.82, 4.74, 4.65, 4.55-4.40, 4.20-4.13, 3.87-3.81 and 3.52-3.49 (7 x m, 7H, H_7, H_8, H_{21}, H_{22} and H_{26}), 3.67 (s, 3H, $COOCH_3$), 3.65, 3.25-3.15 and 3.05-2.95 (3 x m, 2H, OH), 2.55-2.28 (m, 5H), 2.12-1.95 (m, 4H), 1.87-1.44 (m, 8H), 1.32-1.25 (m, 5H), 0.88 (t, J=7.0 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3540 (free OH), 3600-3100 (H-bonded OH), 3100-2820 (C-H), 1725 and 1705 (C=O) cm^{-1}. CI/MS: m/e(%) 461 (0.2, M^++1-H_2O), 443 (0.2, M^++1-2H_2O), 377 (3, M^++1-THPOH), 359 (2, M^++1-H_2O-THPOH), 341 (2, M^++1-2H_2O-THPOH), 85 (100, $C_5H_9O^+$). CI/HRMS m/e 461.2901 [calc.for $C_{27}H_{41}O_6$(M^++1-H_2O): 461.2903].

(12R)-5E,7E-12-hydroxy-10-(tetrahydropyran-2'-yl-oxymethyl)-4-deacetyl-clavulone **47E** *and (12R)-5E,-7Z-12-hydroxy-10-(tetrahydropyran-2'-yl-oxymethyl)-4-deacetyl-clavulone* **47Z**

Elimination of mixture **46a,b**: A solution of **46a,b** (85 mg,) in dichloromethane (5 ml) was treated with excess acetic anhydride (400 mg) and dimethylaminopyridine (100 mg) at room temp. for 3 hrs. The mixture was then poured into dichloromethane (50 ml) and washed with brine (3x), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (n-hexane/ethyl acetate = 3/1) gave pure product **47E** (65

mg, 70 %) and **47Z** (20 mg, 21 %) as colorless oils.

47E: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H, H_{11}), 6.91 (d, $J_{6,7}$=11.8 Hz, 1H, H_7), 6.54 (dd, $J_{6,7}$=11.8 Hz, $J_{5,6}$=15.0 Hz, 1H, H_6), 6.20 (dt, $J_{5,6}$=15.0 Hz, $J_{4,5}$=7.0 Hz, 1H, H_5), 5.49 (ddd, $J_{14,15}$=10.9 Hz, $J_{14,13a}$=7.0 Hz, $J_{14,13b}$=8.0 Hz, 1H, H_{14}), 5.16 (dt, $J_{14,15}$=10.9 Hz, $J_{15,16}$=6.8 Hz, 1H, H_{15}), 4.66 (m, 1H, $H_{2'}$), 4.56-4.50 and 4.29-4.20 (2 x m, 2H, $H_{1'}$), 3.83 and 3.50 (2 x m, 2H, $H_{6'}$), 3.67 (s, 3H, $COOCH_3$), 2.99 A of AB (dd, $J_{13a,b}$=14.2 Hz, $J_{13a,14}$=7.0 Hz, 1H, H_{13a}), 2.71 B of AB (dd, $J_{13a,b}$=14.2 Hz, $J_{13b,14}$=7.0 Hz, 1H, H_{13b}), 2.37-2.26 (m, 4H, H_4 and H_{16}), 2.05-1.85, 1.85-1.70, 1.70-1.47 and 1.30-1.15 (4 x m, 19H), 0.87 (t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3100-2820 (C-H), 1730 and 1695 (C=O), 1630 (C=C, conj.) cm^{-1}. EI/MS: m/e(%) 358 (7, M^++1-AcOH-THP), 85 (100, $C_5H_9O^+$). CI/HRMS m/e 358.2145 [calc.for $C_{22}H_{30}O_4$(M^++1-AcOH-THP): 358.2144].

47Z: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, $J_{6,7}$=11.5 Hz, $J_{5,6}$=15.3 Hz, 1H, H_6), 7.39 (s, 1H, H_{11}), 6.55 (d, $J_{6,7}$=11.3 Hz, 1H, H_7), 6.20 (dt, $J_{5,6}$=15.3 Hz, $J_{4,5}$=7.1 Hz, 1H, H_5), 5.50 (ddd, $J_{14,15}$=10.9 Hz, $J_{14,13a}$=7.5 Hz, $J_{14,13b}$=7.1 Hz, 1H, H_{14}), 5.20 (dt, $J_{14,15}$=10.9 Hz, $J_{15,16}$=6.8 Hz, 1H, H_{15}), 4.67 (m, 1H, $H_{2'}$), 4.51 and 4.24 AB (2 x d, $J_{a,b}$=14.9 Hz, 2H, $H_{1'}$), 3.83 and 3.51 (2 x m, 2H, $H_{6'}$), 3.67 (s, 3H, $COOCH_3$), 2.91 A of AB (dd, $J_{13a,b}$=14.2 Hz, $J_{13a,14}$=7.1 Hz, 1H, H_{13a}), 2.67 B of AB (dd, $J_{13a,b}$=14.2 Hz, $J_{13b,14}$=7.5 Hz, 1H, H_{13b}), 2.40-2.22 (m, 4H, H_4 and H_{16}), 2.05-1.90, 1.90-1.70, 1.70-1.45 and 1.35-1.20 (4 x m, 19H), 0.87 (t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3100-2820 (C-H), 1730 and 1690 (C=O), 1630 (C=C, conj.) cm^{-1}. EI/MS: m/e(%) 502 (0.6, M^+), 443 (9, M^+-AcO), 359 (25, M^+-AcOH-THP), 85 (100, $C_5H_9O^+$). CI/HRMS m/e 502.2932 [calc.for $C_{29}H_{42}O_7$(M^+): 502.2930].

Elimination of mixture **46c,d**: A solution of **46c,d** (150 mg,), excess acetic anhydride (1 ml) and dimethyl-aminopyridine (300 mg) in benzene (10 ml) was stirred at 80^{0}C for 24 hrs. The mixture was then poured into ether (50 ml) and washed with brine (3x), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (hexane/ethyl acetate = 3/1) gave pure product **47E** (75 mg, 44 %) and **47Z** (20 mg, 12 %) as a colorless oils.

(-)-(12R)-5E,7E-10-(Hydroxymethyl)-4-deacetyl-clavulone **48E**

A solution of **47E** (85 mg) in acetic acid (4 ml) and water (1 ml) was stirred at room temp. for 4 hrs. The solution was then poured into ethyl acetate (30 ml) and washed with aq. NaCl (3x). After drying ($NaSO_4$) and concentration *in vacuo*, flash chromatography (n-hexane/ethyl acetate = 2/1) gave product **48E** (35 mg, 50%) as an oil.

48E: $[\alpha]_D^{25}$= -2.8^0 (c=1.11, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H, H_{11}), 6.92 (d, $J_{6,7}$=11.8 Hz, 1H, H_7), 6.54 (dd, $J_{6,7}$=11.9 Hz, $J_{5,6}$=15.0 Hz, 1H, H_6), 6.23 (dt, $J_{5,6}$=15.0 Hz, $J_{4,5}$=7.0 Hz, 1H, H_5), 5.50 (dt, $J_{14,15}$=10.9 Hz, $J_{14,13}$= ~7.4 Hz, 1H, H_{14}), 5.17 (dt, $J_{14,15}$=10.9 Hz, $J_{15,16}$=7.8 Hz, 1H, H_{15}), 4.46 (s, 2H, $H_{1'}$), 3.67 (s, 3H, $COOCH_3$), 2.97 A of AB (dd, $J_{13a,b}$=14.4 Hz, $J_{13a,14}$=7.2 Hz, 1H, H_{13a}), 2.71 B of AB (dd, $J_{13a,b}$=14.2 Hz, $J_{13b,14}$=8.0 Hz, 1H, H_{13b}), 2.48 (s, 1H, OH), 2.37-2.27 (m, 4H, H_4 and H_{16}), 2.07-1.92 (m, 5H), 1.85-1.76 (m, 2H), 1.34-1.20 (m, 6H), 0.88 (t, J=7.1 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, H-dec., $CDCl_3$): δ 193.3/173.5/169.4 (quat.), 150.6 (tert), 146.8 (quat.), 146.7/134.7 (tert), 134.5 (quat.), 131.5/125.3/121.3 (tert.), 84.4 (quat.), 57.7 (sec.), 51.5 (prim.), 35.5/33.2/32.6/31.5/29.0/27.4/23.7/22.5 (sec.), 21.4/14.0 (prim.). IR (CH_2Cl_2): ν 3600 (free OH), 3600-3020 (H-bonded OH), 3100-2820 (C-H), 1735 and 1700 (C=O), 1635 (C=C, conj.) cm^{-1}. CI/MS: m/e(%) 419 (5, M^++1), 359 (48,

M^+-$OCOCH_3$), 341 (67, M^+-H_2O-$OCOCH_3$), 43 (100, $^+COCH_3$). EI/HRMS m/e 418.2357 [calc.for $C_{24}H_{34}O_6(M^+)$: 418.2355].

(-)-(12R)-5E,7Z-10-(Hydroxymethyl)-4-deacetyl-clavulone **48Z**

A solution of **47Z** (30 mg) in acetic acid (4 ml) and water (1 ml) was stirred at room temp. for 4 hrs. The solution was then poured into ethyl acetate (30 ml) and washed with aq. NaCl (3x). After drying ($NaSO_4$) and concentration *in vacuo*, flash chromatography (n-hexane/ethyl acetate = 2/1) gave product **48Z** (12 mg, 50%) as an oil.

48Z: $[\alpha]_D^{25}$= -1.5^0 (c=0.26, CH_3OH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, $J_{5,6}$=15.4 Hz, $J_{6,7}$=11.4 Hz, 1H, H_6), 7.31 (s, 1H, H_{11}), 6.55 (d, $J_{6,7}$=11.3 Hz, 1H, H_7), 6.13 (dt, $J_{5,6}$=15.3 Hz, $J_{4,5}$=7.0 Hz, 1H, H_5), 5.51 (dt, $J_{14,15}$=10.8 Hz, $J_{14,13}$= ~7.3 Hz, 1H, H_{14}), 5.22 (dt, $J_{14,15}$=10.8 Hz, $J_{15,16}$=7.5 Hz, 1H, H_{15}), 4.45 (s, 2H, $H_{1'}$), 3.67 (s, 3H, $COOCH_3$), 2.89 A of AB (dd, $J_{13a,b}$=14.1 Hz, $J_{13a,14}$=7.0 Hz, 1H, H_{13a}), 2.66 B of AB (dd, $J_{13a,b}$=14.2 Hz, $J_{13b,14}$=7.4 Hz, 1H, H_{13b}), 2.40-2.23 (m, 5H, OH, H_4 and H_{16}), 2.08-1.94 (m, 5H), 1.84-1.76 (m, 2H), 1.30-1.15 (m, 6H), 0.88 (t, J=7.1 Hz, 3H, CH_3). IR (CH_2Cl_2): ν 3600 (free OH), 3600-3040 (H-bonded OH), 3100-2820 (C-H), 1730 and 1695 (C=O), 1630 (C=C, conj.) cm^{-1}. CI/MS: m/e(%) 419 (4, M^++1), 359 (19, M^+-$OCOCH_3$), 341 (26, M^+-H_2O-$OCOCH_3$), 43 (100, $^+COCH_3$). EI/HRMS m/e 418.2357 [calc.for $C_{24}H_{34}O_6(M^+)$: 418.2355].

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(*Received in UK* 23 *February* 1995; *revised* 21 *March* 1995; *accepted* 23 *March* 1995)