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Reviews

The Bicyclo[3.2.0]heptan-*endo*-2-ol and Bicyclo[3.2.0]hept-3-en-6-one Approaches in the Synthesis of Grandisol: The Evolution of an Idea and Efforts to Improve Versatility and Practicality

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Abstract:

In this paper we will disclose a chemistry story that started with a single molecule, the monoterpene grandisol, used in protecting cotton crops from an important pest, *Anthonomus grandis* Boheman. Initially, efforts were aimed at giving ever more practicality, versatility, and efficiency to a synthetic scheme that was centered on the key role of the 2,5-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol, available from intermolecular photocyclization and methylation or, better and more conveniently, by an intramolecular copper(I)-catalyzed photobicyclization of the 3,6-dimethylhepta-1,6-dien-3-ol. We have developed an enantiospecific synthesis of both enantiomers of grandisol although some drawbacks would preclude scale up and commercialisation. The major limits of this original single-target synthetic scheme are pointed out along with the changed landscape resulting from recent developments in the fields of bioorganic chemistry and entomology. These changes prompted the elaboration of a new strategy focused on the conception and the development of a practical and efficient preparation bicyclo[3.2.0]hept-2-en-6-ones. The "bicyclo[3.2.0]hept-2-en-6-one approach" stems from a very convenient and general preparation, without photochemical steps, of bicyclo[3.2.0]hept-2-en-6-ones. These compounds proved to be amenable to selective manipulations to prepare not only grandisol but also other important molecules such as lineatin, filifolone, and raikovenal in multitarget and versatile synthetic schemes. Moreover, through resolution of the bicyclo[3.2.0]hept-2-en-6-ones, the procedures can be used to produce enantiomerically pure products. The bismethylation of the carbon atom adiacent to the carbonyl group as well as the conversion into the corresponding unsaturated bicyclic lactones are two important reactions that amplify the potential utility of bicyclo[3.2.0]hept-2-en-6-ones. Their peculiar reactivity, ascribed to the fact that the carbonyl group and the carbon−carbon double bond are attached to the same bridge-head carbon atom, has been demonstrated by the high chemio-, regio-, and stereoselectivity of the NBS-induced lactonization.

One aim of synthetic organic chemistry is to provide for society those compounds that improve or sustain life in its multifaceted aspects and necessities. Over the past decades, by addressing these challenges, synthetic organic chemists have developed the central science, chemistry, in all of its fields and aspects, in a fascinating way. Many highly efficient procedures have been devised which allow the preparation of complex molecules with excellent chemo-, regio-, diastereo-, and enantioselectivity. However, today it is still important to have versatile structures to use as starting materials for a multitude of target molecules that are to be synthesized in a practical fashion. These versatile structures may be considered as good building blocks on which to build up more complex structures. Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity. The aim of this review is to depict an *idea* which stems from a synthetic scheme born to obtain exclusively (single-target oriented synthesis) racemic grandisol **1**, via the bicyclo[3.2.0]-heptan-*endo*-2-ol **2**, and the evolution towards a more ambitious project that allowed for synthesis of several different and synthetically versatile cyclobutane structures and important derivatives through an effective and practical synthesis of bicyclo[3.2.0]hept-3-en-6-ones such as **3**. The creation of many bonds, rings, and stereocenters in a single transformation, seen as a necessary condition for high synthetic efficiency, will be highlighted. The account compiles our findings together with relevant work of other laboratories that used the same key intermediates and/or methodologies related to our strategies.

1. The Bicyclo[3.2.0]heptan-2-ol Approach

Interest in the bicyclo[3.2.0]heptan-*endo*-2-ol (**2**) became prominent in our group during the late 1970s, when we faced the need for a practical synthesis of racemic *grandisol* (cis-2-isopropenyl-1-methylcyclobutan-1-yl ethanol, **1**).[1]

At that time, grandisol (**1**) was already well known to synthetic organic chemists for its unusual *cis*-1,2-trisubstituted cyclobutane structure with two chiral centres and two

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(1) It is interesting that the *trans* isomer is also a natural product that was later isolated from the roots of *Artemisia fragrans* Willd and termed fragrantol (Bohlmann, F.; Zdero, C.; Faass, U. *Chem. Ber.* **1973**, *106*, 2904−2909). The *trans* isomer was found to be 100- to 200-fold less active than the *cis* in the laboratory assay of weevil attraction (see: Martin, T.; Rodriguez, M.; Martin, V. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1151−1164).

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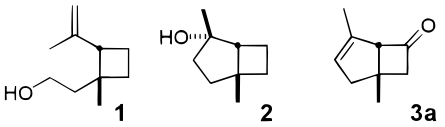
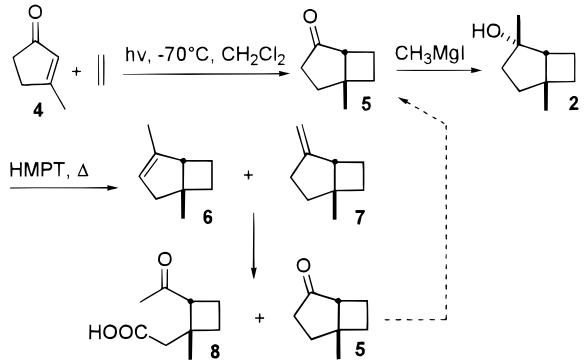


different functional groups. In 1969, this monoterpene was identified[2] as the more important and interesting component of the four synergistic constituents of "grandlure", the sex pheromone of male cotton boll weevils, *Anthonomus grandis* Boheman, an important pest of cotton crops in the U.S.A. Since its discovery, the synthesis of grandisol became a challenge for many organic chemists and has resulted in several ingenious processes.[3] In 1971 J. Tumlinson[4] and coworkers provided an unambiguous synthesis of racemic grandisol (**1**) to confirm the assignment of its structure and later the elegant synthesis of Hobbs and Magnus[5] starting from (−)-*β*-pinene assigned the (1*R*,2*S*)-stereochemistry to (+)-grandisol, the natural enantiomer component of grandlure. When we started our project in 1978 the problem of structural assignment was already solved, and the main interest was in devising a practical and efficient procedure to prepare grandisol at an adequate scale and cost to be used in the control of the pest.

1.1. The Intermolecular Photocycloaddition Route to Racemic Grandisol. Almost all of the stereoselective multistep syntheses described up to that time were lengthy and involved the formation of undesired isomers and by-products. Three of these procedures[6−8] had *cis*-(+)-2-acetyl-1-methylcyclobut-1-yl acetic acid (**8**) as the key intermediate that was efficiently converted into **1**. In their strategy, Cargill and Wright[9] used light to perform a [2 + 2] cycloaddition reaction between 3-methylcyclopent-2-enone (**4**) and ethene at low temperature in dichloromethane, thus accomplishing the simultaneous introduction of two contiguous stereocenters and a new four-membered ring. The stereochemistry of this bicyclic ketone **5** offered us the opportunity of developing a new and practical conversion of **5** into racemic grandisol (**1**) by a novel route[10] described in Scheme 1. The main aspects of our procedure are centered on the synthesis of

Scheme 1. **The main features of the stereoselective synthesis of racemic grandisol by the bicyclo[3.2.0]heptan-*endo*-2-ol**



cis-2,5-dimethylbicyclo[3.2.0]hept-2-ene (**6**) and its conversion into **1** via the intermediate **8**. The reaction of *cis*-fused bicyclic ketone **5** with methylmagnesium iodide afforded the corresponding tertiary alcohol **2** in 92% yield. However, repeated attempts, with different methodologies, to perform the dehydration reaction failed, and we always observed the fragmentation of **2** and the formation of reaction mixtures with several components inconsistent with the desired bicyclic alkene **6**. However, the large variety of known methodologies for effecting dehydration helped us to succeed in our aim. From the outset it was clear that dehydration of the bicyclic and tertiary alcohol **2** must occur exclusively according to an E_2 mechanism to avoid the formation of an intermediate carbonium ion that could undergo rearrangements. We successfully accomplished the dehydration following Monson's procedure,[11] by which **2** was efficiently converted into a mixture of the isomeric bicyclic alkenes **6** and **7** when a solution of it in hexamethylphosphoric triamide (HMPT) was heated at 180−190 °C for 0.5 h and then slowly distilled at ambient pressure under a gentle stream of nitrogen. The temperature of the mixture was carefully maintained just under the boiling point of HMPT. A distillate (boiling point 130−137 °C) was collected consisting of the desired **6** and **7** together with the dimethylamine generated from the reaction of **2** with HMPT. The crude olefinic material was easily obtained in nearly quantitative yield by removal of diethylamine and was shown to be a 7:3 mixture of the *endo*-(**6**) and *exo*-(**7**) isomeric alkenes by the ^{1}H NMR spectrum of the mixture. Several factors cooperated to make this dehydration procedure both efficient and practical. Among these factors were the values of the boiling points of each component (HMPT, the bicyclic alcohol **2**, the bicyclic olefins **6** and **7**, and dimethylamine) and the temperature at which the reaction of compound **2** and HMPT takes place. The low boiling point of dimethylamine, the side-product of this conversion, allowed for the shift of the equilibrium towards the quantitative formation of alkenes simply by continuously removing this volatile amine from the reaction flask.

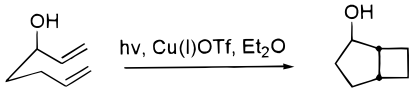
Other significant points about the procedure depicted in Scheme 1 are that the oxidative cleavage performed on the mixture of isomeric olefins **6** and **7** gave a mixture of keto-acid **8** and the bicyclic ketone **5** without epimerization of

(2) Tumlinson, J. H.; Hardee, D. D.; Gueldner, R. C.; Thompson, A. C.; Hedin, P. A. *Science* **1969**, *166*, 1010−1012.
(3) (a) For an excellent illustration of the problems concerning insect pheromones and progressive evolution of the synthetic methodologies used in the synthesis of grandisol up to 1976: Katzenellenbogen, J. A. *Science* **1976**, *194*, 139−148. For more updated reviews, see: (b) Quinkert, G.; Monforts, F.-P.; Ockenfeld, M.; Rhem, D. *Synform* **1983**, *1*, 1−32. (c) Quinkert, G.; Monforts, F.-P.; Ockenfeld, M.; Rhem, D. *Synform* **1985**, *3*, 33−38. (d) For an excellent and authoritative review, see: Mori, K. The Synthesis of Insect Pheromones, 1979−1989. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons Inc.: New York, 1992; Vol. IX.
(4) Tumlinson, J. H.; Gueldner, R. C.; Hardee, D. D.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *J. Org. Chem.* **1971**, *36*, 2616−2621.
(5) Hobbs, P. D.; Magnus, P. D. *J. Chem. Soc., Chem. Commun.* **1974**, 856−857; Hobbs, P. D.; Magnus, P. D. *J. Am. Chem. Soc.* **1976**, *98*, 4594−4600.
(6) Gueldner, R. C.; Thompson, A. C.; Hedin, P. A. *J. Org. Chem.* **1972**, *37*, 1854−1856.
(7) Ayer, W. A.; Bowne, L. M. *Can. J. Chem.* **1974**, *52*, 1352−1278.
(8) Mori, K. *Tetrahedron* **1978**, *34*, 915−920.
(9) Cargill, R. L.; Wright, B. A. *J. Org. Chem.* **1975**, *40*, 120−122. For further significant improvements of the photocyclization reaction of an enone to an alkene, see: Cargill, R. L.; Dalton, J. R.; Morton, G. H.; Caldwell, W. E. *Org. Synth.* **1984**, *62*, 118−124.
(10) Rosini, G.; Salomoni, A.; Squarcia, F. *Synthesis* **1979**, 942−944.
(11) Monson, R. S. *Tetrahedron Lett.* **1971**, 567−570.

the former to the more stable *trans* isomer and that the acid character of **8** made possible a very simple separation from the neutral **5**. The latter was recovered in a sufficiently pure state to be recycled as starting material in a successive preparation, and the conversion of keto-acid **8** into grandisol (**1**) was performed by the straightforward and efficient procedure already reported.

Although the synthetic sequence depicted in Scheme 1 has a number of attractive features, the main limitation of the overall procedure is the initial step of the route, that is, the photochemical [2 + 2] intermolecular cycloaddition[12] between the excited state of 3-methyl-2-cyclopent-2-en-1-one (**4**) and the ground state of ethene. This crucial photochemical reaction must be performed with a double-walled immersion lamp (medium pressure 400-W mercury vapor lamp) equipped with a Pyrex filter and good refrigeration. To effect the conversion of 12 g of starting enone into the bicyclic ketone **5** in 85% yield, the irradiation must be continued for 3 days whilst bubbling ethene into the dichloromethane solution of **4** at very low temperature (−70 °C) to have a sufficiently high concentration of ethene.

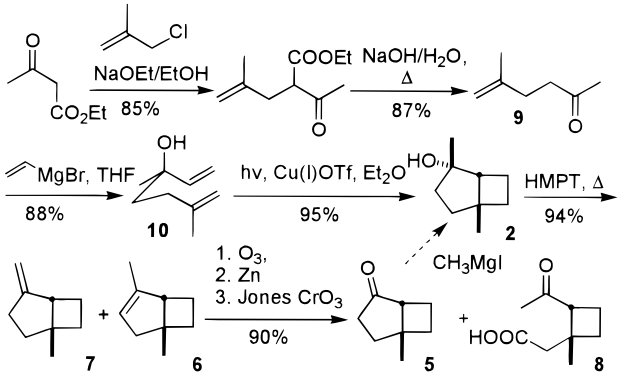
1.2. The Intramolecular Photobicyclization. Our main concern was to maintain or to increase the efficiency of the [2 + 2] photocyclization in the construction of the bicyclic precursor **5** avoiding the afore-mentioned drawbacks. In 1978, just when we started our project, Evers and Mackor[13] first described the intramolecular copper(I)-catalyzed [2 + 2] photocycloaddition of 1,6-diene derivatives (eq 1).



(1)

This reaction was then extensively investigated by Salomon and coworkers,[14] and it is to their credit that they disclosed all of the synthetic potential of this very effective procedure for preparation of bicyclo[3.2.0]heptane derivatives. The reaction is regioselective to 1,6-dieneols, only small amounts of reagents are required, and these are nontoxic. Salomon's methodology was promptly welcomed by us as an appropriate tool for the development of a new procedure for a more convenient preparation of the bicyclic alcohol **2**. Scheme 2 summarizes the overall synthetic pathway we have devised.[15] Methallyl chloride and ethyl acetoacetate are the cheap starting materials used to prepare the unsaturated ketone **9**[16] that was converted into 3,6-dimethylhepta-1,6-dien-3-ol (**10**) by reaction with vinylmagnesium bromide. The intramolecular photobicyclization of this latter compound was accomplished in the presence of copper(I)trifluoromethanesulfonate (CuOTf) as catalyst according to Salomon's

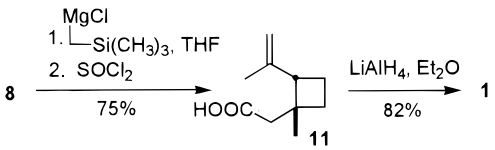
Scheme 2. **The bicyclo[3.2.0]heptan-*endo*-2-ol approach: the improved procedure by an intramolecular copper-catalyzed bicyclization**



procedure. Racemic *cis*-2,5-dimethylbicyclo[3.2.0]heptane-*endo*-2-ol (**2**) was generated stereoselectively in a clean, high-yielding reaction. After 12 h of UV irradiation of 24 g of compound **10** with a Hanovia medium-pressure 450-W mercury lamp using a reactor with quartz vessels, a 95% yield was obtained.

The synthesis of racemic grandisol was then completed by initially producing keto-acid **8** as outlined in Schemes 1 and 2. Subsequent conversion of the acid to grandisol is shown in Scheme 3. Methylenation of the keto-acid **8** was performed using trimethylsilylmagnesium chloride and thionyl chloride[17] and gave compound **11** in 75% yield without any epimerization. Finally lithium aluminum hydride reduc-

Scheme 3. **The conversion of keto-acid 8 into grandisol (1)**



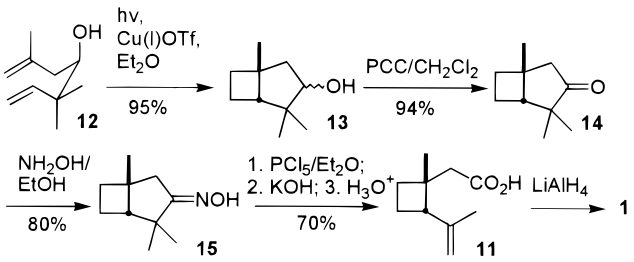
tion in diethyl ether provided racemic grandisol in 31% overall yield based on the starting methallyl chloride or ethyl acetoacetate. Racemic 5-methylbicyclo[3.2.0]heptan-2-one **5**, the only significant side product, could be used again by reaction with methylmagnesium iodide.

Our enthusiasm for this effective use of light to perform the intramolecular [2 + 2] cycloaddition prompted us to apply Salomon's procedure to the preparation of another important bicyclic ketone: 1,4,4-trimethylbicyclo[3.2.0]-heptan-3-one (**14**), claimed as central intermediate for several multistep syntheses[7,18,19] of racemic grandisol. While the conversion of the latter compound into grandisol can be efficiently achieved by a straightforward procedure, all of these syntheses are characterized by difficulties in the preparation of the pure intermediate **14**. Scheme 4 outlines the synthetic sequence we have developed.[20]

The intramolecular [2 + 2] photobicyclization of the homoallylic alcohol 2,5,5-trimethylhept-1,6-dien-ol (**12**, 6g),

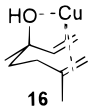
(12) For reviews: Crimmins, M. T.; Reihold, T. L. *Org. React. (N.Y.)* **1993**, *44*, 297; Horspool, W. M. In *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; Royal Society of Chemistry: London, 1986; p 210.
(13) Evers, M. Th. J.; Mackor, A. *Tetrahedron Lett.* **1978**, 821−824.
(14) For reviews, see: (a) Salomon, R. G.; *Tetrahedron* **1983**, *39*, 485−575. (b) Hennig, H.; Rehorek, D.; Archer, R. D. *Coord. Chem. Rev.* **1985**, *61*, 1. (c) Kutal, C. *Coord. Chem. Rev.* **1985**, *64*, 191.
(15) Rosini, G.; Marotta, E.; Petrini, M.; Ballini, R. *Tetrahedron* **1985**, *41*, 4633−4638.
(16) 5-Methyl-5-hexen-2-one (**9**) and copper(I)trifluoromethanesulfonate−benzene complex are commercial products (Aldrich).
(17) Chan, T. H.; Chang, E. *J. Org. Chem.* **1974**, *39*, 3264−3268.
(18) Sonawane, H. R.; Najundiah, B. S.; Udaya Kumar, M. *Tetrahedron Lett.* **1984**, *25*, 2245−2246.
(19) Wenkert, E.; Berges, D. A.; Golob, N. F. *J. Am. Chem. Soc.* **1978**, *100*, 1263−1278.
(20) Rosini, G.; Geier, M.; Marotta, E.; Petrini, M.; Ballini, R. *Tetrahedron* **1986**, *42*, 6027−6032.

Scheme 4. **An alternative use of intramolecular photobicyclization reaction in the stereoselective synthesis of grandisol (1)**

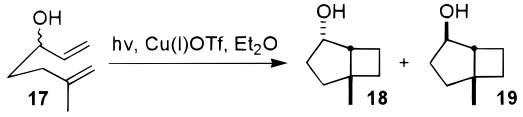


performed in the presence of copper(I)trifluormethanesulfonate (CuOTf) as catalyst, afforded the isomeric bicyclic alcohols **13** in 95%. However, in this case it was necessary to continue the UV irradiation with a Hanovia medium-pressure 450-W mercury vapor lamp for 65 h to observe the complete disappearence of the starting homoallylic alcohol **12**. The mixture of bicyclic alcohols **13** was oxidized to the ketone **14** and the sequence continued with conversion of this into the corresponding oxime **15** by the procedure of Wenkert et al.[19] Finally, the treatment of the oxime with phosphorus pentachloride followed by hydrolysis and subsequent reduction with lithium aluminium hydride provided racemic grandisol with a minimum of intermediate purification.

Although the isomeric *endo*- and *exo*-alcohols **13** are both useful in the synthetic plan outlined in the Scheme 4, it is worth noting to point out the low stereoselection shown in the bicyclization of the homoallylic alcohol **12** when compared with the exclusive formation of the tertiary alcohol **10** in Scheme 2 that occurred in a stereospecific fashion. According to the proposed mechanism[13] the key role of the copper(I)trifluormethanesulfonate (CuOTf) benzene complex as catalyst is associated with its ability to co-ordinate to the hydroxy group and to bring the olefinic residues of the substrate into an ordered disposition ready to undergo bicyclization when irradiated with UV light. With *cis*-2,5-dimethylbicyclo[3.2.0]eptane-*endo*-2-ol (**10**), the transient tridentate species can be described as **16** and afforded the bicyclic alcohol **2** stereospecifically.[21]



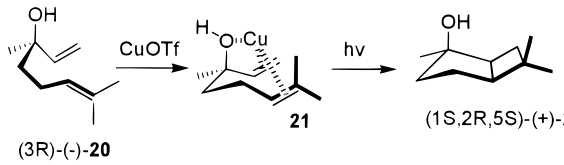
The observed substantial stereospecificity (*endo*:*exo* > 20:1) of the bicyclization of **10** is in sharp contrast with the non stereoselectivity[22] (*endo*:*exo* ≈ 1:1) we observed in the case of racemic 2,5,5-trimethylhept-1,6-dien-ol (**12**) and the low stereoselectivity (*endo*:*exo* ≈ 6:1) reported firstly by Salomon[21] and coworkers and more recently by Langer and Mattay[23] for copper(I)-catalyzed cycloaddition performed on the secondary dienol **17** that gave a mixture of diastereoisomeric bicyclic alcohols **18** and **19** (eq 2).



(2)

Indeed, these results revealed that the presence of a methyl group on the allylic carbon atom bearing the hydroxy group seems to be an important structural feature in assuring the stereospecificity of the intramolecular cycloaddition. Moreover, the location of the hydroxy group between the two olefinic residues on the carbon chain plays an important role, and the structure of the tertiary alcohol **10** better satisfies the structural prerequisite to obtain only one isomer in almost quantitative yield.[20]

It is worth noting that in a stereospecific bicyclization the chiral centre of **10** could induce the formation of two additional and adjacent chiral centres in compound **2**, and even if the original chiral centre was deliberately lost, the new ones would be retained through the whole process and found unchanged in grandisol (**1**).



(3)

The early studies confirmed the hypothesis. The copper(I)-catalyzed bicyclization of racemic linalool gave the corresponding racemic endocyclic alcohol, that was resolved into pure enantiomers with (1*S*,4*R*)-(−)-camphanoyl chloride.[24] The same bicyclization reaction performed with (3*R*)-(−)-linalool (**20**) afforded an optically active bicyclic alcohol **22** that was demonstrated to be enantiomerically pure and to which the absolute configuration (1*S*,2*R*,5*S*)-(+) was assigned[25] on the basis of the tridentate ligand **21** being the intermediate species that underwent photobicyclization (eq 3). With these results in hand, the time was ripe to attempt the synthesis of enantiomerically pure (+)-**6** and (−)-**2**. The enantioselective synthesis of both the enantiomers of those key intermediates could open the route to a practical and effective preparation of (+)-**1**, the grandlüre component, and of the other enantiomer (−)-**1** also.

1.3. An Efficient Resolution of *cis*-2,5-Dimethylbicyclo-[3.2.0]heptane-*endo*-2-ol (2). Small amounts of both enantiomers of compound **2** were first obtained by optical resolution[25] through the use of (1*S*,4*R*)-(−)-camphanoyl chloride as resolving agent. However, fractional crystalliza-

(21) For a detailed illustration of the stereoselectivity of copper(I)-catalyzed photobicyclization of 1,6-heptadien-3-ols: Salomon, R. G.; Coughlin, D. J.; Ghosh, S.; Zagorsky, M. G. *J. Am. Chem. Soc.* **1982**, *104*, 998−1007. See also: Salomon, R. G.; Ghosh, S. *Org. Synth.* **1984**, *62*, 125−133.

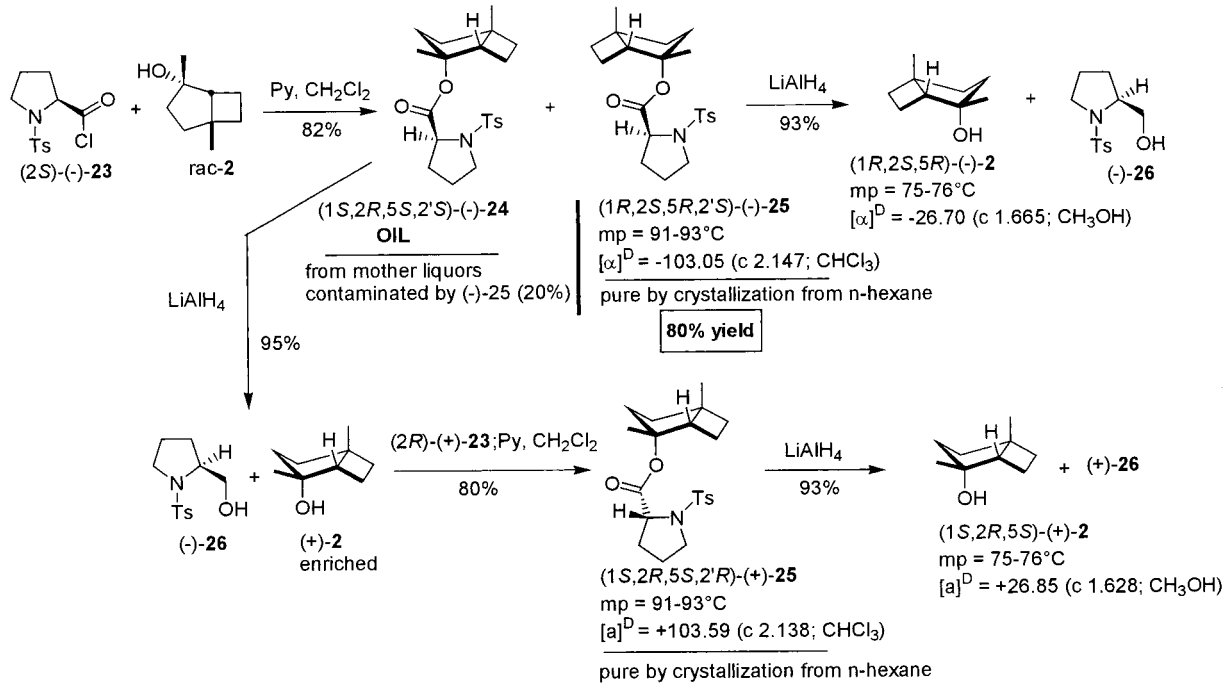
(22) The low or non-existent stereoselectivity of the copper(I)-catalyzed photobicyclization of 1,6-heptadien-4-ols has been ascribed to the apparent lack of preference between the tridentate coordination with Cu(I) of this hydroxydiene ligand in a boat-like conformation and the bidentate coordination that does not involve the hydroxy group but retains a chair-like arrangement. See: refs 13 and 21.

(23) (a) Langer, K.; Mattay, J. *J. Org. Chem.* **1995**, *60*, 7256−7266. (b) Langer, K.; Mattay, J.; Heidbreder, A.; Möller, M. *Liebigs Ann. Chem.* **1992**, 257−260.

(24) (a) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587−1593. (b) Gerlach, H.; Kappes, D.; Boeckman, R. K., Jr.; Maw, G. N. *Org. Synth.* **1992**, *71*, 48−55.

(25) Rosini, G.; Carloni, P.; Iapalucci, M. C.; Marotta, E. *Tetrahedron: Asymmetry* **1990**, *1*, 751−758.

Scheme 5. **The methodology for the resolution of racemic *cis*-2,5-dimethylbicyclo[3.2.0]heptane-endo-2-ol (2)**



tion of the diastereoisomeric camphanates of **2** proved to be difficult and time-consuming. Moreover, camphanic acid cannot be recovered and recycled. Soon afterwards, whilst looking for a method to be run on an economic scale, we chose proline as the lead compound for the synthesis of chiral auxiliaries, and after a systematic study, (2*S*)-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic acid chloride [(2*S*)-(−)-NTP chloride, (−)-(**23**)] was identified as an apt resolving agent. This (2*S*)-proline derivative (−)-(**23**) together with its enantiomer allowed for a practical and inexpensive resolution[26] of alcohol **2** as depicted in Scheme 5. By this procedure an efficient preparation and separation of the enantiomers (−)-**25** and (+)-**25** in good yields was achieved. These enantiomers underwent separate lithium aluminium hydride cleavage in tetrahydrofuran giving enantiomerically pure (−)-**2** and (+)-**2** together with the corresponding enantiomerically pure prolinols (−)-**26** and (+)-**26**. These latter compounds could be easily converted into the corresponding optically active carboxylic acids by oxidation and reused as resolving agents. It must be pointed out that it is the levorotatory bicyclic alcohol (−)-**2** which is the precursor of (+)-grandisol, the enantiomer of grandisol naturally occurring in grandlure, and that is the less expensive enantiomer of proline, the (2*S*)-(−)-proline, which is required for its resolution and purification.

1.4. The Enantiospecific Synthesis of *cis*-2,5-Dimethylbicyclo[3.2.0]eptane-*endo*-2-ol (2) by the Chiron Approach. The enantiospecific synthesis, or EPC synthesis,[27] of both the enantiomers of **10** following the "Chiron Approach",[28] was achieved[22] by exploiting the structural analogy between dienol **10** and linalool (Figure 1). Scheme 6 summarizes the synthetic pathway by which the structural architecture of (*R*)-(−)-linalool was modified to obtain (−)-**10** with retention of the chiral centre, and then how this was converted into the desired enantiomerically pure bicyclic alcohol (+)-**2** by intramolecular photobicyclization. The utility of the trimethylsilyl-protecting group in the sequence is noteworthy. It was introduced under mild reaction conditions, and shown to be sufficiently robust to survive exposure to ozono, Grignard reagent, and Wittig reagent, but it was readily converted to the original hydroxy group by treatment with potassium hydrogen carbonate in methanol.

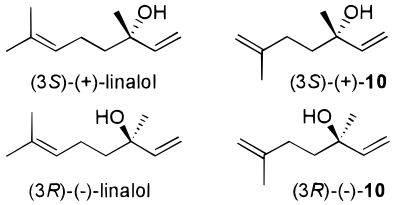


Figure 1. **Optically active linalools and the structural analogies with tertiary allylic alcohols 10.**

The monoterpene alcohol linalool occurs in nature in both dextrorotatory (coriandol) and levorotatory (licareol) forms as constituents of essential oils.[29] However, while natural (3*R*)-(−)-linalool is commercially available with ee > 96%, the enantiomeric excess of the other commercially available natural enantiomer is only 64%. The same synthetic sequence depicted in Scheme 5 for the preparation of (+)-**2** gave (−)-**2**

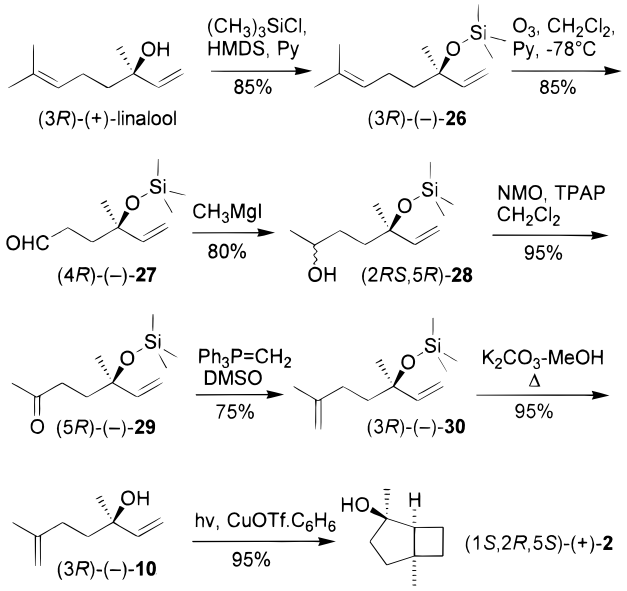
(26) Rosini, G.; Marotta, E.; Raimondi, A.; Righi, P. *Tetrahedron: Asymmetry* **1991**, *2*, 123−138.

(27) Seebach, D.; Hungerbuhler, E. Syntheses of Enantiomerically Pure Compounds (EPC-Syntheses). In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag; Berlin, 1980; p 91.

(28) For an authoritative presentation and illustration of this strategy, see: Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983.

(29) Bauer, K.; Garbe, D. *Common Fragrance and Flavor Materials. Preparation, Properties, and Uses*; VCH Verlagsgesellschaft mbH: Weinheim, 1985.

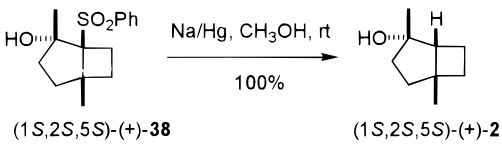
Scheme 6. **The enantiospecific synthesis of (1*S*,2*R*,5*S*)-(+)-*cis*-2,5-dimethylbicyclo[3.2.0]heptane-*endo*-2-ol (2) from (3R)-(+)-linalool according to the Chiron approach**



(ee = 64%), the precursor of the dextrorotatory grandisol, when we used (3*S*)-(+)-linalool (ee = 64%). In this case, the enriched levorotatory sample of **2** has been purified by esterification with (2*S*-(−)-NTP chloride [(−)-**23**] and crystallisation of the major diastereoisomeric component (−)-**25** from *n*-hexane as depicted before.

Again, it is important to point out that it is the less expensive enantiomer of proline is required for the purification, and this fact counterbalances the lower optical purity of (3*S*)-(+)-linalool commercially available as a natural product. Moreover, both the enantiomers of linalool can be prepared from enantiomerically pure α-pinenes by an industrial procedure devised by Ohloff[30] et al that gives (+)- and (−)-linalool with optical purity greater than 93%.

More recently, Monteiro and Zukerman-Schpector[31] have described another synthesis of (+)-**2** and (+)-grandisol (**1**) (Scheme 7) following the Chiron Approach. The key step of this *nonphotochemical* synthesis is a rhodium catalyzed intramolecular carbenoid cyclization of α-diazo-*β*-ketosulfone (*R*)-**34** readily available from (+)-citronellol, another important component from Nature's chiral pool. The synthetic sequence afforded an enantiomerically pure cyclopentanone derivative (+)-**38**. With the aim to confirm the structure, this latter intermediate was efficiently converted into the (+)-**2** by quantitative desulfuration (eq 4).

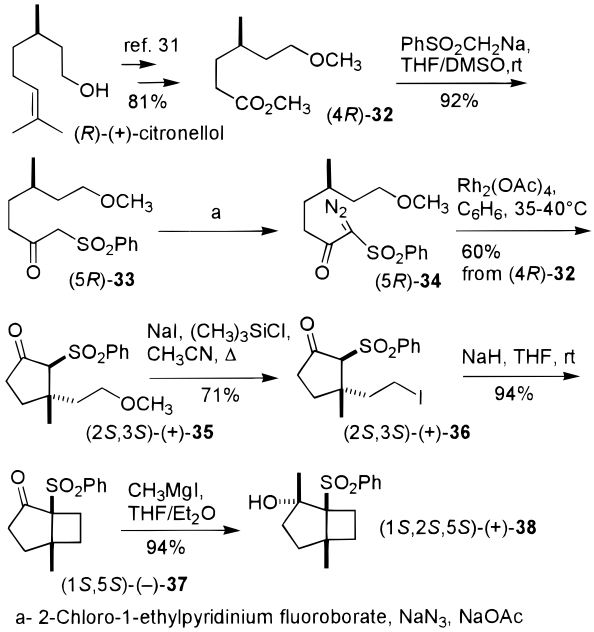


(4)

Despite the existence of a proven procedure for conversion (+)-**2** into (−)-**8**, the authors completed their synthesis using an independent route (as shown in Scheme 8) that starts from

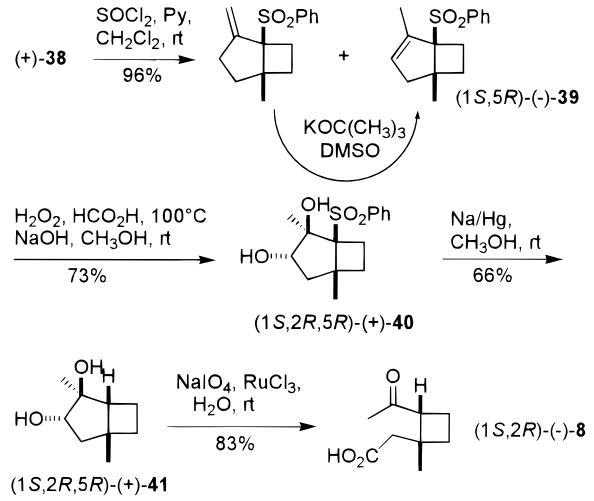
(30) Ohloff, G.; Klein, E.; Schade, G. U.S. Patent 3,240,821, 1966.
(31) Monteiro, H. J.; Zukerman-Schpector, J. *Tetrahedron* **1996**, *52*, 3879.

Scheme 7. **The Monteiro and Zukerman−Schpector synthesis using the Chiron approach**



the efficient dehydration of the tertiary alcohol (+)-**38** to give a 1:1.4 mixture of two crystalline isomeric alkenes.

Scheme 8. **The final part of the Monteiro and Zukerman−Schpector synthesis of (+)-grandisol**



Base-catalyzed isomerization of this mixture gave the more stable endocyclic isomer (−)-**39** in high yield.

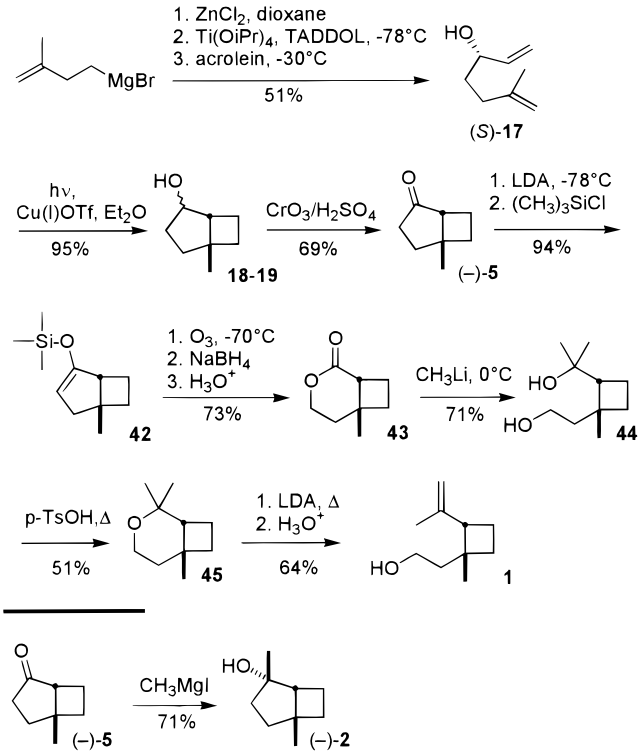
Monteiro and Zukerman-Schpector's synthesis is ingenuous in its use of the α-diazo-*β*-ketosulphone intramolecular cyclization as an alternative to the photochemical reaction. Furthermore, the highly crystalline nature of the intermediates helps in the necessary purification stages. However, the length of the synthesis and a need of purification of intermediates means that it is still inferior to the photochemical routes.

1.5. The Enantiospecific Preparation of *cis*-2,5-Dimethylbicyclo[3.2.0]eptane-*endo*-2-ol (2) by Asymmetric Synthesis. In the last decade the scope of academic and industrial organic synthesis has been profoundly extended by developments in the field of catalytic asymmetric synthesis. The wide

variety of reaction processes that can be catalyzed by soluble transition-metal complexes and the ease with which such complexes can be modified with chiral ligands creates manifold opportunities for the development of new stereocontrolled reaction processes. After having shown the stereospecificity of the copper(I)-catalyzed bicyclization which ensures chirality transfer from (−)-**10** to (+)-**2**, and the easy conversion of this latter into (+)-grandisol, our attention was focused on the development of an effective and practical asymmetric synthesis of enantiomerically pure dienol **10** for the preparation of enantiomerically pure grandisol.

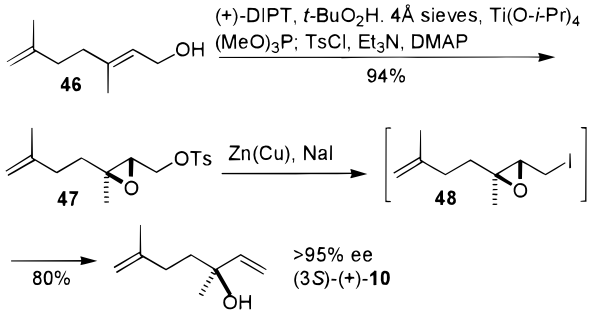
Recently, Langer and Mattay[23] have reported the preparation of (*S*)-6-methyl-1,6-heptadien-3-ol (**17**) by the titanate-catalyzed enantioselective addition to acrolein of a dialkenylzinc compound generated in situ from the corresponding Grignard reagent (Scheme 9). In this efficient enantioselective addition devised by Seebach[32] et al, titanium tetraisopropoxide and (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetranaphth-2-yl-1,3-dioxolane-4,5-dimethanol (TADDOL) give rise to the spirotitanate that acts as chiral catalyst. The dienol (*S*)-**17** was converted into the bicyclic alcohols **18** and **19** by irradiation in the presence of copper(I) trifluoromethanesulfonate−benzene complex (CuOTf), and GLC-analysis of these latter compounds revealed an enantiomeric excess > 98% for both. To determine the absolute configuration, the diastereoisomer **18** was converted into (−)-**2** with known stereochemistry and absolute configuration (Scheme 9) after having performed the separation of diastereoisomers by semipreparative HPLC (cyclohexane/ethyl acetate 85:15). In this case also, the authors devised a novel route to grandisol (**1**) in which the bicyclic ketone plays the role of key intermediate as outlined in Scheme 9.

Scheme 9. **Mattay's preparation of (+)-grandisol by asymmetric synthesis**



The proven efficiency of the copper(I)-catalyzed intramolecular bicyclization of 3,6-dimethylhepta-1,6-dien-3-ol (**10**) to obtain *cis*-2,5-dimethylbicyclo[3.2.0]heptane-*endo*-2-ol (**2**) clearly moves the key problem of the enantiospecific synthesis of this latter compound to the choice of a good method for preparation of the desired enantiomer of the dienol **10**. The efficient and practical synthesis of optically active allylic tertiary alcohols from the 2,3-epoxyalkan-1-ols *p*-toluenesulfonate **47** by the in situ formation of the epoxyiodides **48** and their subsequent reduction with a zinc−copper couple[33] (Scheme 10) is an excellent procedure, developed recently and that also works well in large-scale synthesis. This process, in conjunction with the Sharpless−Katsuki asymmetric epoxidation (SAE),[34,35] allows optically active tertiary allylic alcohol **10** to be prepared without the necessity of a resolution. Either enantiomer may be obtained depending on the chirality of the tartrate ester used in the SAE. In addition, although the procedure developed by German, Lygo, and coworkers proved to be efficient, practical, and convenient, a number of groups[36] have contributed to further develop this methodology.

Scheme 10. **An efficient asymmetric synthesis of optically-active tertiary allylic alcohol (3*S*)-(+)-10**



2. The Major Limits of the Approach, the Modified Landscape and the Hints for a New Synthetic Project

As described above, we have developed a proven, efficient synthesis of racemic grandisol. We have also modified this synthesis so that it can deliver pure forms of either enantiomer. However, there are three limitations to the route which remain to be addressed. These are as follows: (i) the procedure is based on one photochemical step which, although highly efficient and stereoselective, limits its applicability in large scale preparations; (ii) the key step of

(32) Seebach, D.; Behrendt, L.; Felix, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1008−1009. Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321−1323.

(33) Balmer, E.; Germain, A.; Jackson, W. P.; Lygo, B. *J. Chem. Soc., Perkin Trans. I* **1993**, 399−400.

(34) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.

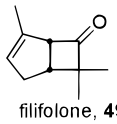
(35) For interesting examples of industrialization of the Sharpless asymmetric epoxidation, see: Shum, W. P.; Cannarsa, M. J. Sharpless Asymmetric Epoxidation: Scale-up and Industrial Production. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley & Sons Ltd.: New York, 1997; p 363.

(36) Habashita, H.; Kawasaki, T.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 2392−2396 and the literature here collected at reference 14 of this paper.

dehydration of the tertiary bicyclic alcohol **2** requires the use of hexamethylphosphoramide (HMPA or HMPT; CAS 680-31-9), which is considered to be a "possible human carcinogen"[37] (OSHA "selected carcinogen"); and finally (iii) the synthesis is restricted to the preparation of grandisol only.

Indeed, as time passed, the reasons for the synthesis of grandisol evolved and assumed more importance and additional interesting features. At the beginning, (+)-*cis*-2-isopropenyl-1-methylcyclobutaneethanol (grandisol, **1**) was known only as the more important component of grandlure, the pheromone blend of *A. grandis* Boheman, an important pest of the cotton crops in the U.S.A. However, it has since been found that grandisol is also released by female ambrosia beetle *Trypodendron signatum* L.,[38] by male bark beetles of the species *Pityophthorus pityographus*,[39] *Pytiogenes quadridens*, and *P. calcaratus*,[40] while grandisol and the respective aldehyde, grandisal, have been identified as pheromones of weevils of the species *Pissodes*.[41] Therefore, today it is possible to claim that grandisol can be considered a molecular "word" present in many insect "languages", inducing behavioural responses in several different species. The importance of this compound is consequently amplified, and the practical synthesis of grandisol assumes more and more economic relevance.

At the same time, several other 1,2-polysubstituted cyclobutane structures were discovered and assumed increased importance. In 1974, the monoterpenoid filifolone (**49b**) was isolated from *Artemisia filifolia* Torrey in the (1*S*,5*S*) form and from *Ziera smithii* Andrews as the (1*R*,5*R*) antipode.[42] Subsequently, filifolone has been identified as a component of the essential oil of *Chrysantemum japonense*[43] and of Moroccan wormwood *Artemisia erba alba*.[44]



filifolone, **49b**

lineatin, **50**

Moreover, in 1977, (+)-lineatin (**50**), another important monoterpenoid, was isolated from the frass of the female ambrosia beetle *Trypodendron lineatum* Olivier,[45] and it was shown to elicit powerful secondary attraction in laboratory and field trials. *T. lineatum* is a deleterious pest to forests, both in Europe and in North America, boring tunnels into the sapwood of a number of coniferous species. Lineatin is also produced by *T. signatum*,[38] together with grandisol, and it was shown that sticky traps containing (+)-lineatin attracted the predator *Thanasimus formicaria*, and more recently, it has been observed that *T. lineatum* is an important prey for *Thanasimus formicaris*.[46]

Until 1990, when we started out new project, the synthesis of racemic filifolone had already been accomplished following different approaches,[47] and over the years, a number of syntheses of racemic and optically active lineatin[48] have been described in the literature. Since that date, several papers have been published from different research groups;[49] however, few procedures have the features that distinguish a process capable of being run on the desired scale in an economic manner.

With this new outlook, we started to explore the possibility of developing a *unified synthetic strategy* that would provide access to several different interesting synthetic targets such as grandisol, filifolone, lineatin, and other interesting targets. Our aim was to develop a procedure which, having no photochemical step and none of the other drawbacks already described, should be both aesthetically satisfying and also commercially more acceptable.

3. The Bicyclo[3.2.0]hept-3-en-6-one Approach: A Unified Synthetic Strategy without Photochemical Steps

At an early stage of our new project, we learned of a similar interest in grandisol and lineatin synthesis by G. Donegani Research Center of ENICHEM S.p.A and members of its research team. As the interactions between our groups have always been amicable and the efforts of both groups were oriented toward the same goal, it was quite natural to agree to work together in an atmosphere of cooperation. Our teams joined forces with the goal of devising a new strategy to develop an efficient, cost-effective process which would be amenable to large-scale processing of several different synthetic targets.

From the outset, the core structure of grandisol and lineatin was perceived to be the *cis*-substituted cyclobutane ring, and 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one (**3**) was viewed as an ideal pivotal intermediate to our targets showing the substitution pattern amenable for a practical and efficient

(37) Because of its carcinogenity, hexamethylphosphoramide should be handled using "basic prudent practices, supplemented by the additional precautions for work with compounds of high chronic toxicity. In particular, this compound should be handled only in a fume hood, using appropriate impermeable gloves and splash goggles to prevent skin and eye contact. Containers of this substance should be stored in secondary containers." Taken from *Prudent Practice in the Organic Laboratory: Handling and Disposal of Chemicals*; National Academic Press: Washington, DC 1995; pp 324−325.

(38) Francke, W.- Convergency and Diversity in Multicomponent Insect Pheromones. In *Advances in Invertebrate Reproduction-4*; Porchet, M.; Audries, J.-C., Dhaimant, A., Eds.; Elsevier Science Publishers: Amsterdam, 1986; pp 327−336.

(39) Francke, W.; Pan, M.-L.; Konig, W. A.; Mori, K.; Puapoomchareon, P.; Heuer, H.; Vité, J. P. *Naturwissenschaften* **1977**, *64*, 98.

(40) Francke, W.; Bartels, J.; Kron, S.; Schulz, S.; Baader, E.; Tengo, J.; Schneider, D. *Pure & Appl. Chem.* **1989**, *61*, 539−542.

(41) Booth, D. C.; Phillips, T. W.; Claeson, A.; Silverstein, R. M.; Lanier, G. N.; Wesr, J. R. *J. Chem. Ecol.* **1983**, *9*, 1−12.

(42) Torrance, S. J.; Steelink, C. *J. Org. Chem.* **1974**, *39*, 1068−1074.

(43) Uchio, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2342−2346.

(44) Benjailali, B.; Sarris, J.; Richard, H. *Sci. Aliments* **1982**, *2*, 515−521.

(45) MacConnell, J. G.; Borden, J. H.; Silverstein, R. M.; Stokking, E. *J. Chem. Ecol.* **1977**, *3*, 549−561.

(46) Tommeras, B. A. *Experientia* **1988**, *44*, 536−537; Tommeras, B. A.; Mustaparta, H. *Naturwissenschaften* **1985**, *72*, 604−606.

(47) Stadler, H.; Rey, M.; Dreiding, A. *Helv. Chim. Acta* **1984**, *67*, 1854−1858 and references therein.

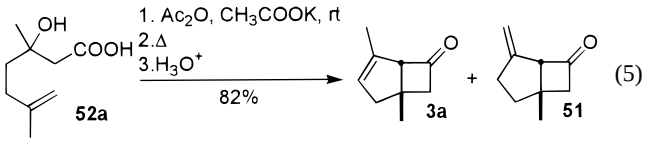
(48) For a complete listing of lineating synthetic studies up to 1989, see: reference 3d.

(49) For elegant syntheses of lineatin published after 1989, see: (a) Mori, K.; Nagano, E. *Liebigs Ann. Chem.* **1991**, 341−344. (b) Hoffmann, N.; Scharf, D. *Liebigs Ann. Chem.* **1991**, 1273−1277. (c) Sonawane, H. R.; naik, V. G.; Bellur, N. S.; Shah, V. G.; Purohit, P. C.; Kumar, M. U.; Kulkarni, D. G.; Ahuja, J. R. *Tetrahedron* **1991**, *38*, 8259−8276. (d) Grandguillot, J.-C.; Rouessac, F. *Tetrahedron* **1991**, *47*, 5133−5148. (e) Narasaka, K.; Kusama, H.; Hayashi, Y. *Bull. Soc. Chim. Jpn.* **1991**, *64*, 1471−1478. (f) Kim, D.; Lee, Y. K.; Jang, Y. M.; Kim, I. O.; Park, S. W. *J. Chem. Soc., Perkin Trans. I* **1990**, 3221−3224. (g) Baeckstrom, P.; Li, L.; Polev, I.; Unelius, C. R.; Wimalisiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358−3362.

conversion into compounds **1**, **49b**, and **50** as well as into several other biologically active compounds. Compound **3a** could be prepared through an intramolecular [2 + 2] cycloaddition of an in situ generated α,β-unsaturated ketene with a terminal double bond.

In 1987, Snider[50,51] reported a novel procedure to prepare bicyclo[3.2.0]heptenone compounds by which the slow addition of a toluene solution of 3,6-dimethyl-2,6-heptadienoic acid chloride to a refluxing solution of triethylamine in toluene gave the bicyclic ketone **51** in 43% yield, and only small and variable yields of **3a**, the isomer with an endocyclic double bond, were observed. More recently, Baeckstrom et al.[52] have reported a procedure by which a mixture of compounds **3a** and **51** was obtained in 62% yield (2:1 ratio) by refluxing a complex mixture of isomeric heptadienoic acids in acetic anhydride and sodium acetate. Both of these methodologies have been used in two formal synthesis of racemic lineatin.

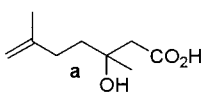
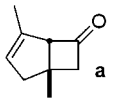
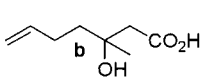
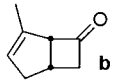
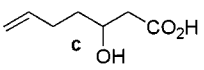
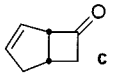
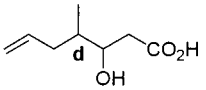
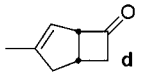
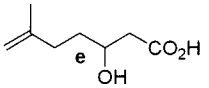
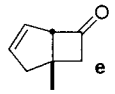
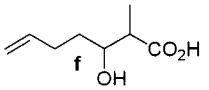
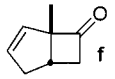
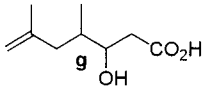
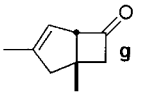
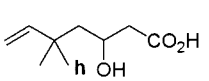
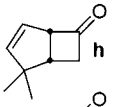
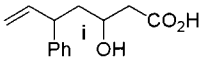
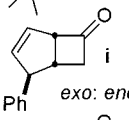
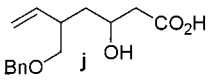
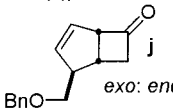
So, with a view to large-scale synthesis, our first challenge was to devise a practical procedure with a better yield of **3a** and with a higher isomeric purity. It was therefore a major advance when we found[53,54] that the treatment of 3,6-dimethyl-3-hydroxy-6-heptenoic acid **52a** with potassium acetate and acetic anhydride at room temperature for 2 h followed by heating for 4 h under reflux gave compound **3a** in 82% yield of isolated product with only 2−5% of the isomer **51** (eq 5).



(5)

Moreover, this procedure proved to be quite practical and almost general. Table 1 summarizes the results obtained by performing this bicyclization reaction with several different 3-hydroxy-6-heptenoic acids **52**.[54] The advantages of our process over those of Snider et al. and Baeckstrom et al. lie in the higher yields and the higher selectivity in favour of the endocyclic isomer **3a**. Further studies[55] have supported a possible mechanism in which a 1,2-elimination occurs as the first step, generating an α,β-unsaturated mixed anhydride which undergoes the 1,4-elimination of acetic acid to give the olefinic α,β-unsaturated ketene. This latter is a transient species which efficiently cyclizes in an intramolecular fashion to generate the bicyclic unsaturated ketones.

Table 1. **Bicyclo[3.2.0]hept-3-en-6-ones (3) by bicyclization of 3-hydroxy-6-heptenoic acids (52)**

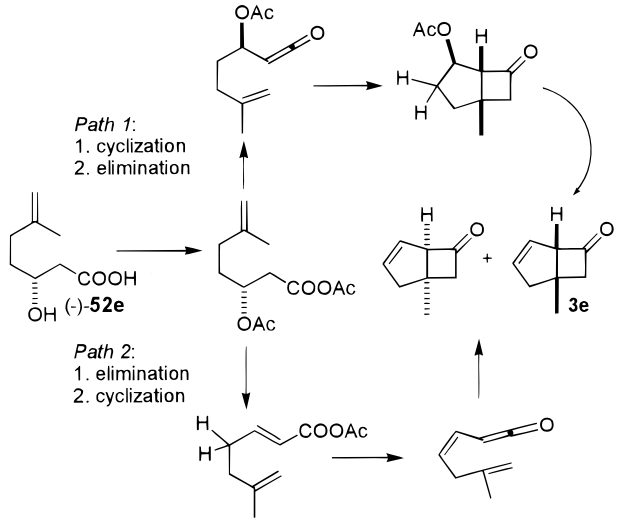
Starting Material (**52**)	Product (3)	Yield (%)
		82
		79
		62
		63
		78
		63
		55
		48
	 *exo*: *endo* = 3:1	60
	 *exo*: *endo* = 3:1	70

This sequence of events would account for the loss of chirality of the starting 3-hydroxy-heptenoic acid. This loss of chirality was demonstrated when of enantiomerically pure 3-hydroxy-heptenoic acid **52e** afforded a racemic bicyclic compound in high yield. Scheme 11 summarizes the alternative pathways for the conversion into bicyclic[3.2.0]hept-3-en-6-one and shows that cyclization followed by elimination would lead to enantiomerically pure product.

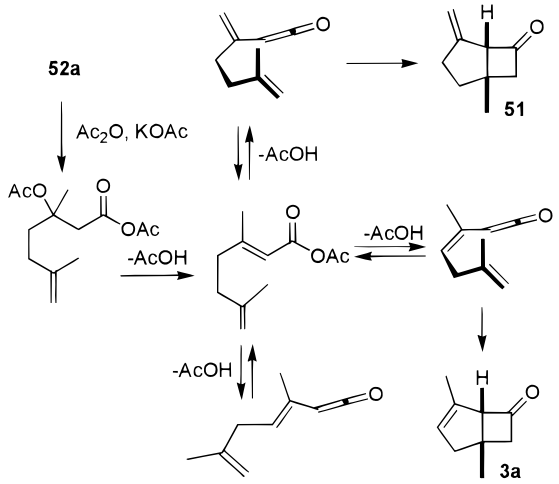
We presumed that the yields observed, substantially higher that those observed by Snider et al. in the treatment of the unsaturated carboxylic acid chlorides with triethylamine, could be ascribed to the game of equilibria involved in the global process by which the thermodynamically more stable isomer, the endocyclic one, was produced in high yield. Scheme 12 portrays this game of equilibria among the different intermediates involved in the process. The acetate anion plays the key role of collecting all of these forms towards the formation of the bicyclic heptenone as if a funnel was active. In terms of yields, it must be considered how

(50) Snider, B. B.; Ron, E.; Burbaum, B. W. *J. Org. Chem.* **1987**, *52*, 5413−5419.
(51) For an excellent review on the intramolecular cycloadditions reactions of ketenes and ketenimminium salts with the olefinic residues, see: Snider, B. B. *Chem. Rev.* **1988**, *88*, 793−811.
(52) Baeckstrom, P.; Li, L.; Polev, I.; Unelius, C. R.; Wimalisiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358−3362.
(53) Rosini, G.; Serra, R.; Rama, F.; Confalonieri, G. -ENICHEM S.p.A.- Istituto Guido Donegani S.p.A.-European Patent Specification n.922001957.5- Publ. n. 0521 571 B1 (13 September 1995).
(54) Rosini, G.; Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P. *Org. Synth.* **1997**, *74*, 158−168.
(55) Marotta, E.; Medici, M.; Righi, P.; Rosini, G. *J. Org. Chem.* **1994**, *59*, 7529−7531.

Scheme 11. **Alternative reaction paths for the conversion of 3-hydroxy-6-heptenoic acids into bicyclo[3.2.0]hept-3-en-6-ones**



Scheme 12. **The equilibrium system in the conversion of 3-hydroxy-6-heptenoic acids into bicyclo[3.2.0]hept-3-en-6-ones**



relevant is the recovery to bicyclization of the 3,4-*E*-unsaturated intermediates that cannot undergo bicyclization. We found that **51** does not convert into **3a** when heated at reflux conditions in acetic anhydride, potassium acetate, and 2 equiv of acetic acid.[55]

The model of bicyclo[3.2.0]hept-2-en-6-one (**3c**) pictured in Figure 2 shows that this small molecule has a rigid skeleton. This compound and substituted analogues of it have

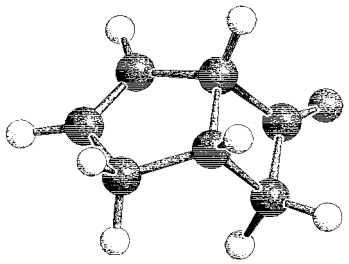


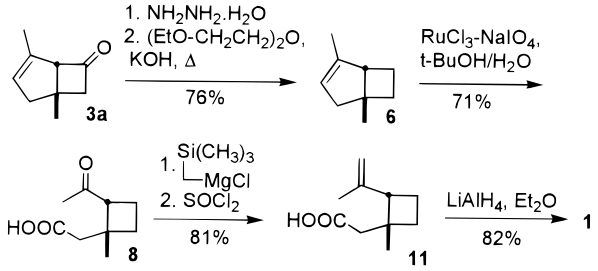
Figure 2. **The spatial picture of the wedge-shaped bicyclo-[3.2.0]hept-3-en-6-one (3c).**

a variety of features that turn out to be of synthetic value. They possess two functionalised fused rings of different sizes, a five-membered ring with a carbon−carbon double bond, and a four-membered ring with a carbonyl group. Moreover they are shaped like a wedge, making possible selective reactions at the less hindered top-side (*exo*-side) both at the double bond and at the carbonyl group. The two functional groups are joined by a strained bridge-head carbon atom. This fact can result in a reactivity that involves both groups at once. Finally, this simple molecule has two chiral centres.[56]

With compound **3a** easily available, we tackled the selective modifications of each ring in order to convert this pivotal intermediate into grandisol (**1**) and lineatin (**50**).

3.1. The Improved Route to Racemic Grandisol. Scheme 13 depicts the conversion of **3a** into racemic grandisol (**1**).[57] The deoxygenation of **3a** by the Huang−Minlon

Scheme 13. **The stereoselective conversion of compound 3a into racemic grandisol (1)**



modification of the Wolff−Kishner reduction is the key step and gave compound **6** which was easily separated and obtained in 76% yield by direct distillation from the reaction mixture.

This step provides a direct link to the synthetic scheme we developed previously and eliminates two of its main limitations: the photochemical step for formation of the bicyclic alcohol **2** and dehydration of **2** to **6** with the dangerous hexamethylphosphoric triamide.

Moreover, the bicyclic alkene **6** obtained from **3a**, has been converted (Scheme 14) into the bicyclic ketone **14**, another key intermediate in several synthesis of racemic grandisol.[7,18−20,58]

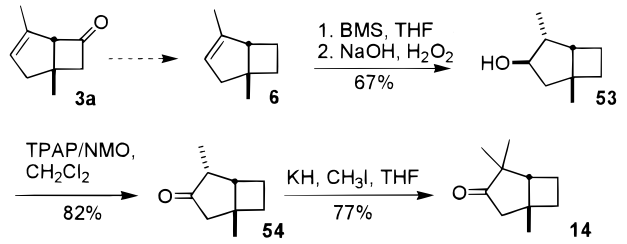
3.2. The Synthesis of Racemic Lineatin. Similarly, the synthesis of racemic lineatin (**50**)[57] takes advantage of the

(56) This bicyclic heptenones have a very close relative: bicyclo[3.2.0]hept-2-en-6-one where the double bond is between C2 and C3 instead of between C3 and C4. Bicyclo[3.2.0]hept-2-en-6-one could be prepared from cyclopentadiene and in situ generated dichlorokene according to a well known procedure (Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363−2364) and is commercially available in enantiomerically pure form also. It has found many applications particularly in the synthesis of prostaglandins. For an overview, see: Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989; pp 249−309. For some other syntheses that used bicyclo[3.2.0]hept-2-en-6-one as starting material or intermediate, see, inter alia: Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 7555−7558; Hirst, G. C.; Johnson, O., Jr.; Overman, L. E.; *J. Am. Chem. Soc.* **1993**, *115*, 2992−2993; Cotterill, I. C.; Jaouhari, R.; Dorman, G.; Roberts, S. M.; Scheinmann, F.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. I* **1991**, 2505−2512.

(57) Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P.; Rosini, G.; Serra, R.; Venturelli, F. *Tetrahedron* **1994**, *50*, 3235−3250.

(58) Sonawane, H. R.; Naik, V. G.; Bellur, N. S.; Shah, V. G.; Purohit, P. C.; Kumar, M. U.; Kulkarni, D.; G.; Ahhuja, J. R. *Tetrahedron* **1991**, *47*, 5133−3148.

Scheme 14. **The conversion of bicyclic alkene 6 into 1,4,4-trimethylbicyclo[3.2.0]heptan-6-one (14)**

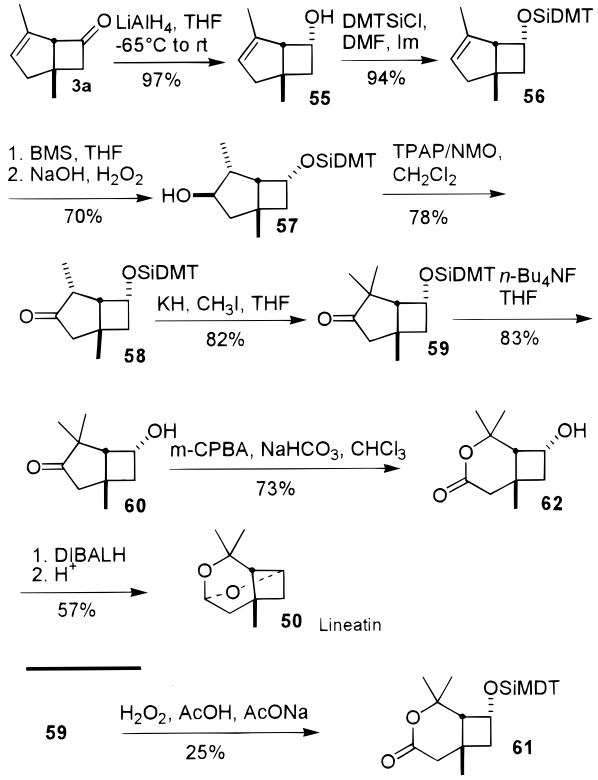


already preformed four-membered ring of compound **3a**, according the synthetic sequence summarized in Scheme 15.

The reduction of the carbonyl group, performed with lithium aluminium hydride in diethyl ether at low temperature (−65 °C), gave the *endo*-alcohol **55** almost exclusively since the hydride selectively comes from the less hindered face. The wedge shape of the molecule allows for the formation of this further chiral centre with the proper stereochemical configuration. Then, the synthesis continues with the manipulation of the five-membered ring after protection of the hydroxy group. Hydroboration of the carbon−carbon double bond and subsequent oxidation forms the methylsubstituted ketone **58**. This was reacted with methyl iodide in the presence of potassium hydride in tetrahydrofuran to give the geminal dimethyl derivative **59** which, when deprotected to give the free hydroxy group, underwent an highly selective oxidation with mCPBA to hydroxylactone **62**. Reduction of this with DIBALH directly afforded racemic lineatin as already reported in the literature.[59] It is worth pointing out that, many attempts to effect the Baeyer−Villiger lactonization directly on **59** in which the hydroxyl group is protected as the dimethyl-*t*-butylsilyl ether failed.[57] Only the reaction using hydrogen peroxide in acetic acid in the presence of sodium acetate gave compound **61** in a 25% yield after 90 h of stirring at room temperature.

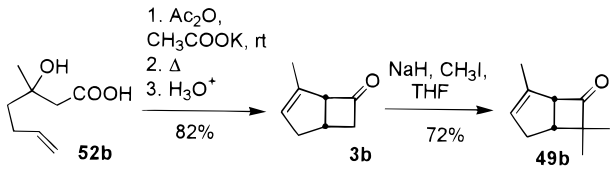
3.3. The Synthesis of Racemic Filifolone. Filifolone (**49b**) is a simple bicyclic monoterpene that incorporates the bicyclo[3.2.0]hept-3-ene-6-one structure and therefore, in principle, could be formed directly by cyclization of 3,7-dimethyl-3-hydroxy-6-octenoic acid. However, this gave a multitude of products. Among them it was possible to identify 4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-one (**49b**, filifolone) in only 20−30% yield, and its isolation and purification proved to be very difficult. To overcome this limitation, we have addressed the problem of the geminal dimethylation of C7 of bicyclo[3.2.0]hept-3-en-6-ones. This conversion has been performed through the generation of thermodynamically more stable enolates with sodium hydride in tetrahydrofuran in the presence of an excess of methyl iodide. The reaction turned out to be a general reaction, and several other dimethyl derivatives could be prepared, although yields are not always satisfactory. Table 2 summarizes the results obtained by using this methodology. As far as the synthesis of racemic filifolone is concerned, a successful and practical procedure[60] stems from an efficient preparation

Scheme 15. **The stereoselective synthesis of racemic lineatin (50) by using the pivotal bicyclic ketone 3a**



of 4-methylbicyclo[3.2.0]hept-3-en-6-one (**3b**) followed by the geminal C7 bismethylation as depicted in Scheme 16.

Scheme 16. **Two-step synthesis of filifolone (49b)**



3.4. The Synthesis of the Marine Sesquiterpenoid Raikovenal. As a natural extension of our studies on the utilization of the bicyclo[3.2.0]hept-3-en-6-one approach in organic synthesis we faced the total synthesis of racemic raikovenal (**63**), a marine sesquiterpenoid isolated by Pietra and co-workers[61] from marine ciliate *Euplotes raikovi* Amagaliev, collected along Atlantic coast near Casablanca. The authors assigned the structure and the relative stereochemistry of **63** on the basis of extensive NMR studies. At first sight it was evident that the main part of the molecular array of raikovenal is the bicyclo[3.2.0]heptane core with the five-carbon side chain containing alcohol and α,β-unsaturated aldehyde groups in a strictly defined geometric configuration. The stereoselective synthesis of racemic raikovenal proceeded through the application of the bicyclization methodology according to the plan outlined in Scheme 17.[62,63]

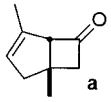
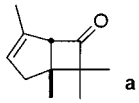
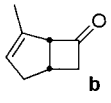
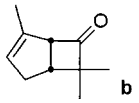
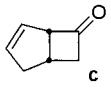
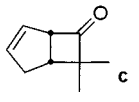
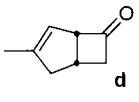
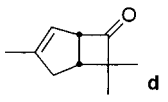
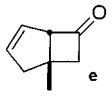
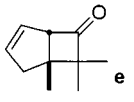
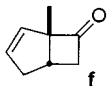
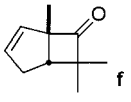
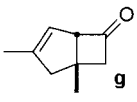
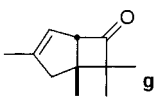
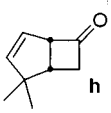
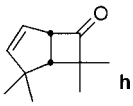
(59) Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron* **1983**, *39*, 1735−1743.

(60) Marotta, E.; Pagani, I.; Righi, P.; Rosini, G. *Tetrahedron* **1994**, *50*, 7645−7656.

(61) Guella, G.; Dini, F.; Erra, F.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1994**, 2585−2586.

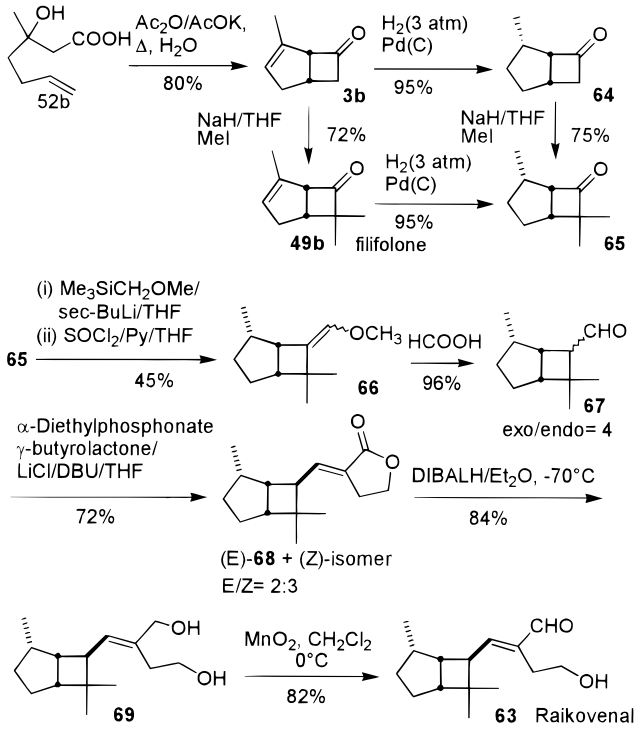
(62) Rosini, G.; Laffi, F.; Marotta, E.; Pagani, I.; Righi, P. *J. Org. Chem.* **1998**, *63*, 2389−2391.

Table 2. **Bismethylation of bicyclo[3.2.0]hept-3-en-6-ones**

Starting Material (**3**)	Product (**49**)	Yield (%)
 **a**	 **a**	62
 **b**	 **b**	72
 **c**	 **c**	58
 **d**	 **d**	41
 **e**	 **e**	59
 **f**	 **f**	38
 **g**	 **g**	75
 **h**	 **h**	50

3-Hydroxy-3-methyl-6-heptenoic acid (**52b**) was treated with acetic anhydride in the presence of potassium acetate to generate the bicyclic intermediate **3b**, already used as precursor in the synthesis of racemic filifolone (**49b**). The palladium-catalyzed hydrogenation of the bicyclic unsaturated ketone **3b** followed by bismethylation of the C7 gave the 4-endo-7,7-trimethylbicyclic derivative dihydrofilifolone (**65**). Alternatively, compound **65** could be obtained by palladium-catalyzed hydrogenation of filifolone (**49b**). The carbonyl homologation of dihydrofilifolone (**65**) to obtain the aldehyde **67** proved to be the crucial step of this synthetic sequence. In situ generation of the Magnus reagent and subsequent reaction at low temperature with ketone **65** gave a mixture of diastereoisomeric β-alkoxysilane intermediates. Treatment of this mixture with thionyl chloride and pyridine provided the diastereoisomeric enolethers **66** in 45% yield. Hydrolysis with formic acid gave the designed aldehyde **67** which underwent a stereoselective olefination with α-(diethylphosphonato)-γ-butyrolactone according to the Horner−Wadsworth−Emmons (HWE) modification as used by Masamune, Roush et al.,[64] to give an isomeric mixture of (*E*) and (*Z*)-**68** (*E*:*Z* = 2:3). The (*E*)(*Z*) mixture of **68** was

Scheme 17. **The stereoselective total synthesis of racemic raikovenal (63) through the bicyclo[3.2.0]hept-3-en-6-one approach**



reduced using DIBALH, and the diol **69** was easily separated from the product mixture by flash chromatography. The synthesis was completed by the selective oxidation of the allylic alcohol of **69** which afforded racemic raikovenal (**63**) in 82% yield. In principle, the (*Z*)-**68** isomer could be recycled to the aldehyde **67** by an oxidative cleavage of the carbon−carbon double bond, thus compensating, to some extent, for the low yield of the homologation.

3.5. An Efficient and Practical Method for the Resolution of Bicyclo[3.2.0]hept-3-en-6-ones. From the outset it was evident that the synthetic potential of bicyclo[3.2.0]hept-3-en-6-ones would be greatly enhanced if a method of resolution could be developed. It was already observed that the mechanism of the bicyclization precludes the chiral synthesis of bicyclo[3.2.0]hept-3-en-6-ones starting from enantiomerically pure 3-hydroxy-6-alkenoic acids.

Successive studies[65] were focused on those unsaturated bicyclic ketones **3a**, **3b**, and **49b** already used as intermediates in the stereoselective synthesis of racemic grandisol (**1**), lineatin (**50**), filifolone (**49b**), and raikovenal (**63**) and the corresponding *endo*-alcohols **55**, **70**, and **71**. Indeed, single crystal X-ray diffraction analysis of the camphanic acid esters helped us to assign the absolute configuration of the enantiomers of these latter bicyclo[3.2.0]hept-3-en-*endo*-6-ols (Table 3). These bicyclic alcohols were easily obtained enantiomerically pure by: (i) the stereoselective reduction of the bicyclo[3.2.0]hept-2-en-6-ones when treated with $LiAlH_4$ in THF at −70 °C and allowing the temperature to

(63) Several months before the publication of our paper a very similar synthesis of raikovenal has appeared in the literature: Snider, B. B.; Quing Lu *Synth. Commun.* **1997**, *27*, 1583−1600.

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(65) Marotta, E.; Pagani, I.; Righi, P.; Rosini, G.; Bertolasi, V.; Medici, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2319−2328.

(66) Gerlach, H. *Helv. Chim. Acta* **1985**, *68*, 1815−1821; Gerlach, H.; Kappes, D.; Boekman, K., Jr.; Maw, G. N. *Org. Synth.* **1993**, *71*, 48−55.

Table 3. **Optical properties and absolute configurations of some bicyclo[3.2.0]hept-3-en-endo-6-ols and bicyclo[3.2.0]hept-2-en-6-ones**

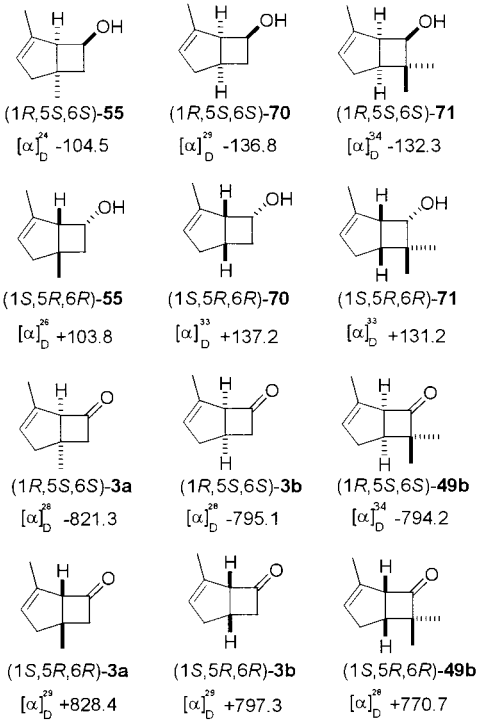
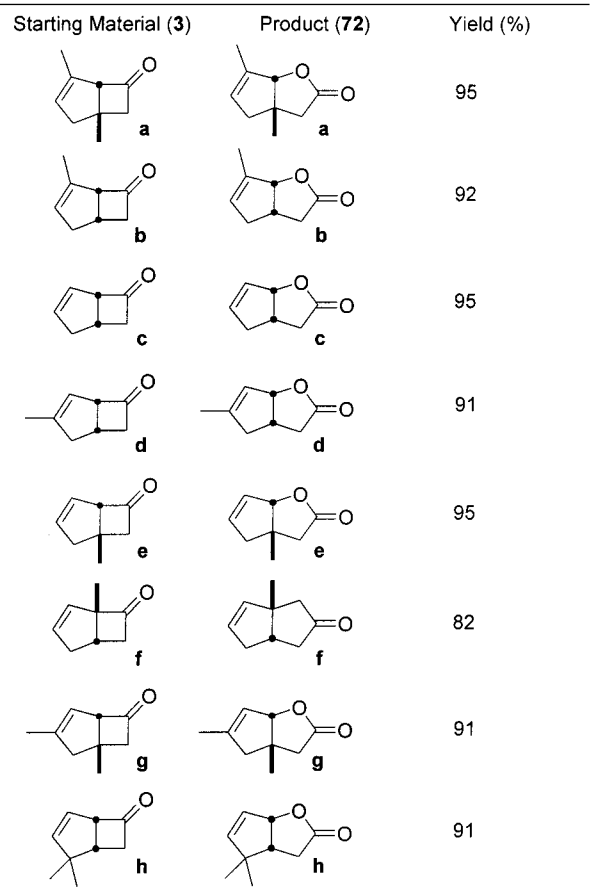


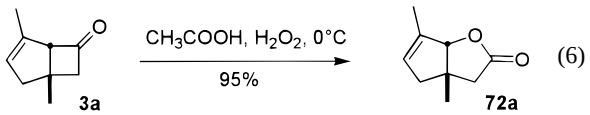
Table 4. **The conversion of bicyclo[3.2.0]hept-3-en-6-ones (3) into the corresponding lactones 72**



rise to rt; (ii) the efficient conversion into diastereoisomeric pairs using (−)-(1*S*,4*R*)-camphanic acid chloride[66] as resolving agent in pyridine at 0 °C, (iii) a practical separation of diastereoisomers by a single flash chromatography with silica gel and eluting with dichloromethane alone and, finally, (iv) a mild alkaline hydrolysis. Then, the conversion into enantiomerically pure bicyclo[3.2.0]hept-2-en-6-ones was performed by oxidation with tetra-*n*-propylammonium perruthenate (TPAP) using *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant.[67] The optical rotations we have recorded using enantiomerically pure samples of compounds **3a**, **3b**, and **49b** (filifolone) give the true dimension of the rotational strengths of these compounds. The magnitudes of the rotational strengths of these optically pure bicyclo[3.2.0]hept-3-en-6-ones are consistent with the geometric structures of this type of unsaturated ketone chromophore, in which the overlap of the olefinic π and π^* orbitals create an intense charge-transfer band and the overlap of non bonded p and olefinic π orbitals causes the coupling of the transitions.[68]

It is worth pointing out that the resolution of compounds **3a**, **3b**, and **49b** (filifolone) as well as of the corresponding *endo*-alcohols **55**, **70**, and **71** into their enantiomerically pure forms, allowed the bicyclo[3.2.0]hept-3-en-6-one approach to be applicable to the synthesis of both enantiomers of grandisol (**1**), filifolone (**49b**), lineatin (**50**), and raikovenal (**63**) and of several other potential synthetic targets. Moreover, these studies have paved the route to a systematic study of the use of microorganisms for more effective and practical resolution of these promising substrates.[69,70]

3.6. Chemioselective Baeyer−Villiger Lactonization of Bicyclo[3.2.0]hept-3-en-6-ones. The convenient and practical synthesis of bicyclo[3.2.0]hept-3-en-6-ones **3** opened a new route to 3,3a,4,6a-tetrahydro-2H-cyclopenta[*b*]furan-2-ones **72**, another important class of compounds. It consists of regioselective Baeyer−Villiger oxidation[71] of the former compounds to generate the allylic lactones **72** in a process that proved to be highly chemioselective[72] (eq 6).



(6)

The conversion of bicyclo[3.2.0]hept-3-en-6-ones **3** into the unsaturated bicyclic lactones **72** was carried out using 30% hydrogen peroxide in 90% acetic acid at 0 °C for 6−12h. The results obtained are collected in Table 4 and so far indicated this to be a general procedure, superior to the more

(67) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13−19.
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(71) For an excellent review on the Baeyer−Villiger oxidation of ketones, see: Strukul, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1198−1209.
(72) Marotta, E.; Righi, P.; Rosini, G. *Tetrahedron Lett.* **1994**, *35*, 2949−2950. Marotta, E.; Pagani, I.; Rosini, G. *Tetrahedron* **1994**, *50*, 7645−7656.

traditional methods used to prepare 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one **72c** and its 3a-, 5-, and 6a-methyl derivatives (**72b** and **72d**−**e**). These materials have been used as valuable precursors in the elegant synthesis of Curran et al. of linear condensed triquinane sesquiterpenes, such as hirsutene,[73] $\Delta^{9,(12)}$-capnellene,[74] hypnophilin, and coriolin,[75] by a tandem radical cyclization.[76]

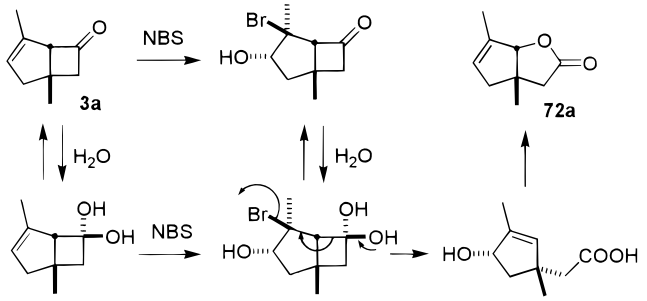
3.7. The Peculiar Reactivity of Bicyclo[3.2.0]hept-3-en-6-ones with *N*-Bromosuccinimide. The appealing structure of bicyclo[3.2.0]hept-3-en-6-ones 3 with two fused rings of different size, each functionalized in a different manner, thus allowing for chemio-, regio-, and stereoselective transformations have all of these mainfold aspects in common with the well-known isomeric bicyclo[3.2.0]hept-2-en-6-ones.[56] However, bicyclo[3.2.0]hept-3-en-6-ones 3 have, in addition, a special relationship between the two functional groups. In fact, the two functional groups are closer than in the case of bicyclo[3.2.0]hept-2-en-6-ones, and the sp^2 carbon atom of the carbonyl group and one of the sp^2 carbon atoms of the carbon−carbon double bond are connected by one of the sp^3 carbon atoms, and this last also occupies a bridgehead position. This significant difference has been already evidenced by the sharp differences in magnitude of the optical rotations of the pure enantiomers of these latter compounds, compared to the isomeric bicyclo[3.2.0]hept-2-en-6-ones. Moreover, it was correctly supposed that both functional groups might exhibit a characteristic combined reactivity.

In this context, we found that treatment of 1,4-dimethylbicyclo[3.2.0]hept-2-en-6-ones (**3**) with *N*-bromosuccinimide (NBS) in aqueous dimethoxyethane (DME) at 0 °C, afforded the lactones **72** resulting in a new method for the selective oxidation of a cyclobutanone carbonyl group to the corresponding lactone (Scheme 18).[77]

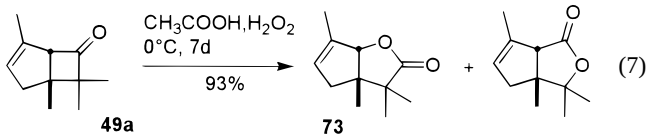
With 4-methyl-substituted bicyclo[3.2.0]hept-2-en-6-ones the fragmentation occurred spontaneously at 0 °C to give the corresponding lactones **72** in high yield. With 4-unsubstituted substrates the intermediate halohydrin could be isolated and the corresponding lactone obtained although in lower yields, by heating the reaction mixture to 60 °C.

Among the more relevant features of this alternative lactonization procedure is a better regioselectivity observed in those cases in which a competition between two Baeyer−Villiger rearrangements is possible. For example, the hydrogen poeroxide oxidation of **49a**, at 0 °C in acetic acid, is complete in 7 days affording, in a comparable yield, a 7:3 mixture of the two regioisomeric lactones in a 93% yield

Scheme 18. **The peculiar reactivity of bicyclo[3.2.0]hept-3-en-6-ones (i.e., 3a) with NBS in aqueous DME**



(eq 7); with NBS the same oxidation can be achieved in 30 min at 0 °C and selectively gave the isomer **73**.



(7)

These results support the assumption introduced before by which the reactivity of bicyclo[3.2.0]hept-3-en-6-ones should not be regarded simply as the sum of the reactivities of the two isolated functionalities as occurs in the case of isomeric bicyclo[3.2.0]hept-2-en-6-ones but as a single moiety which arises from this peculiar disposition of the two functional groups.

Conclusions

The chemistry above described shows the main features of the "bicyclo[3.2.0]heptan-*endo*-2-ol approach" and then those of the "bicyclo[3.2.0]hept-2-en-3-one approach". The first approach is a single-target oriented procedure with an important photochemical step. The latter is a multitarget approach without any photochemical step. The results here depicted, together with the ready availability of bicyclo[3.2.0]-hept-2-en-3-ones, bodes well for an ever increasing use of these important compounds in organic synthesis. Further studies are to be devoted to implementation of the chemistry of bicyclo[3.2.0]hept-2-en-3-ones and amplification of their use as versatile chiral building blocks in the organic synthesis of more complex molecules.

Acknowledgment

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