

Chiral building blocks based on technical grade β -citronellene

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Abstract - (+)- β -Citronellene, the main component of the technical grade pyrolysate of (+)-cis-pinane, can be chemoselectively processed to certain C₁₀ derivatives in the presence of isomeric C₁₀ olefins. These derivatives are converted into mono- and bifunctional chiral building blocks suitable for the incorporation of \sim MeCH \sim fragments with R- or S-configuration into aliphatic chains. Although their optical purity may be as low as 50%, that of the end products can be upgraded by inclusion of an optical resolution step in the synthetic sequence.

INTRODUCTION

Due to the different reactivity of its double bonds, β -citronelle is a good chiral building block (CBB). Both of its enantiomers, S-(+)-1 and R-(-)-1, are manufactured from (+)- α - or (-)- α -pinene, respectively. However, their use in the EPC-synthesis (ref. 1) remains, so far, limited for two reasons: (i) Insufficient optical purity of α -pinenes in the majority of turpentine oils brings about the same drawback in the resulting β -citronellene; (ii) In industry, S-1 or R-1 have to be separated from the isomeric hydrocarbons produced from (+)-cis-pinane (2) or its (-)-enantiomer upon thermolysis. That implies the need for careful fractionation and, consequently, enhanced cost.

Chemoselective extraction of S-1 or R-1 from a technical grade pyrolysate of cis-pinane (TGPP or "technical grade β -citronellene") could reduce the cost of chiral building blocks (CBBs) derived from it. Moreover, the products thus obtained would be more suitable for the control and upgrading of optical purity than the parent diolefin.

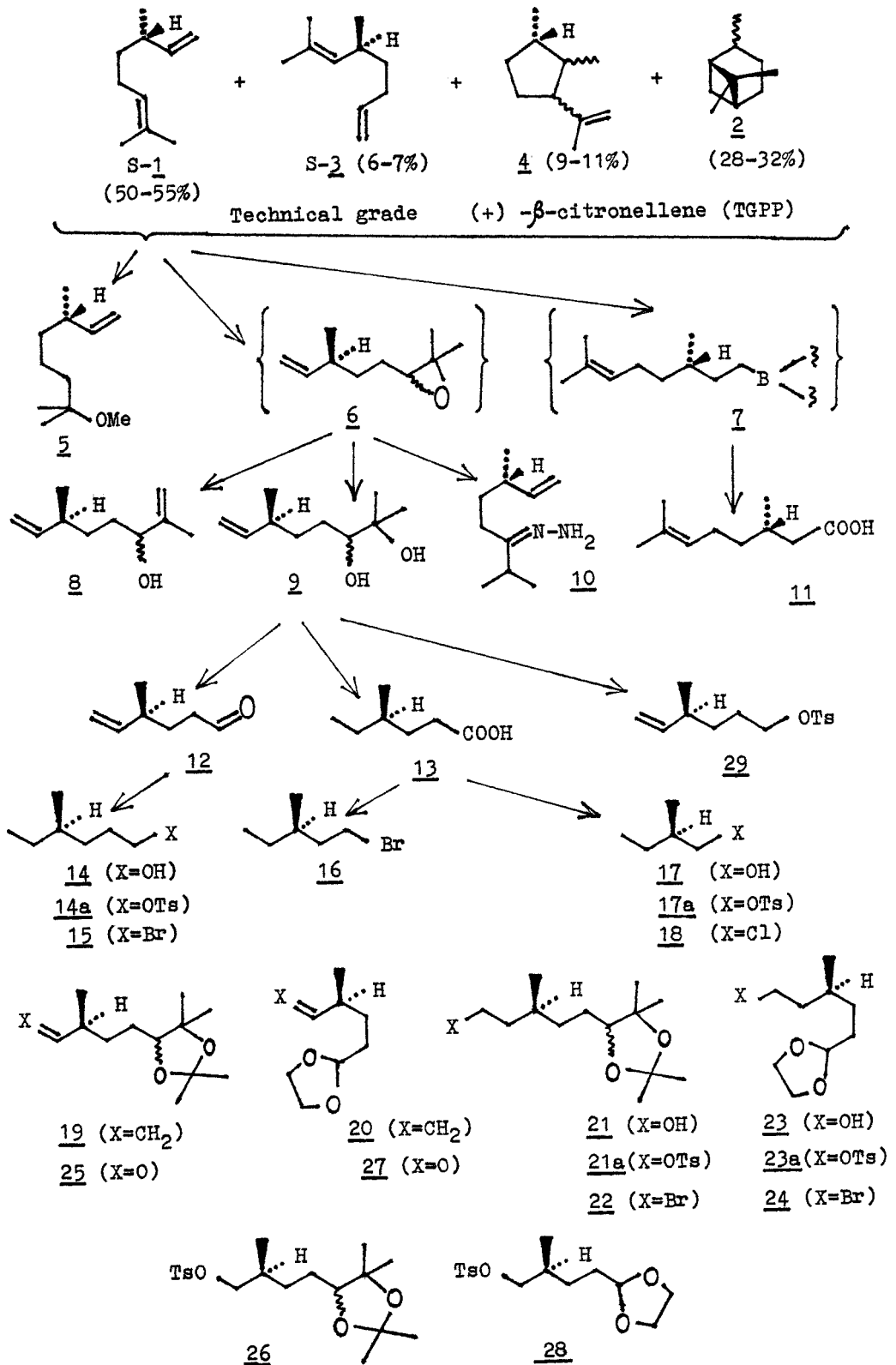
PREPARATION OF CHIRAL BUILDING BLOCKS

C₁₀ Blocks. We elaborated several variants of chemoselective transformation of S-1 in the presence of isomeric hydrocarbons (S-3, 4, cis/trans-2) which provide easy separation of the products from the unreacted components of the dextrorotatory TGPP (Scheme 1). Thus, a known procedure (ref. 2) was modified to give the methoxy alkene 5 in ca. 45% yield (based on the content of S-1 in TGPP). Broader opportunities are opened by the formation of the epoxide 6 (0.95-1.10 eqv of a peracid per 1 eqv of S-1 in the TGPP). Without isolation, it was isomerized to the 3R,6S-dienol 8 which was separated from the unreacted hydrocarbons by distillation (ref. 3). Still better, the acid hydrolysis of 6 results in the 3S,6R diol (9) which is isolated simply by distilling off all the more volatile components of the reaction mixture (ref. 4). Yet another procedure is to transform the raw epoxide 6 into S-3,7-dimethyl-1-octene-6-one (cf. ref. 1a) and from there to the corresponding hydrazone (10). Finally, direct oxidation of the organoborane 7 as described for the synthesis of alkanolic acids from terminal alkenes (ref. 5) affords S-citronellic acid (11) in 40-42% yield.

C₉, C₇, C₆, and C₅ Blocks. All of them were obtained from the easily available diol 9. First, it was converted to a number of monofunctional CBBs of general type EtCHMe(CH₂)_nX (where X is an oxygen-bearing function or halogen atom and n=1-3). S-4-Methyl-5-hexenal (12) and R-4-methylhexanoic acid (13) served as intermediates from which other C₇, C₆, and C₅ blocks with R-configuration were prepared.

Still wider is the set of bifunctional CBBs derived from diol 9 or aldehyde 12. Thus, hydroboration of the double bond in the O-isopropylidene derivative 19 or in the acetal 20 opens the way to the CBBs of C₁₀ group (21, 21a,

Scheme 1

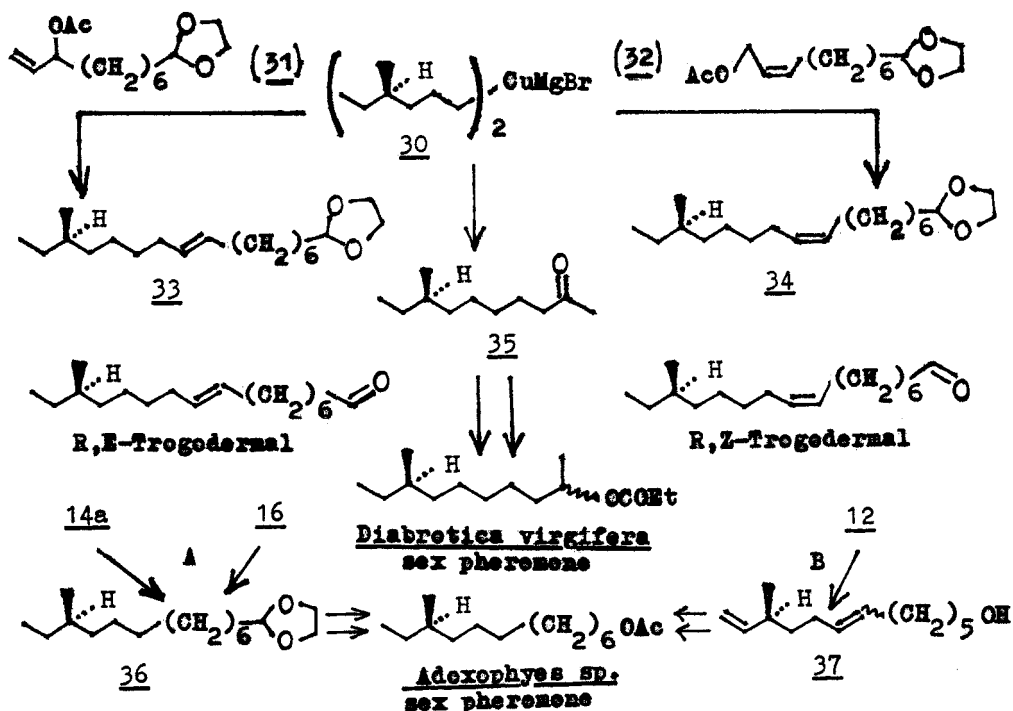


22) or C7 group (23,23a,24), respectively, while its oxidative cleavage leads to the CBBs of C9 or C6 groups (25,26 or 27,28). The unsaturated C7-tosylate 29 is obtained from 9 in three steps. Due to their bifunctionality these CBBs can be used for the incorporation of a chiral \sim CHMe \sim fragment into a target molecule either in R- or in S-configuration.

APPLICATION TO THE SYNTHESIS OF NON-RACEMIC COMPOUNDS

Pheromones with one chiral centre In our synthesis of R,E- and R,Z-trogoderms, the two sex pheromones of khapra beetle, bromide 15 via organocuprate 30 was coupled with the allylic acetates 31 or 32. In the first case (Scheme 2) a clean S_N2' reaction took place. In the second, the ratio of S_N2 and S_N2' coupling products was ca. 93:7, so acetal 34 had to be chromatographed before its conversion to Z-trogodermal (ref. 6). The reaction of organocuprate 30 with 3-buten-2-one affords ketone 35, from which 8R-methyl-2RS-decyl propionate, the sex pheromone of *Diabrotica virgifera* beetle, was obtained (ref. 7). R-10-methyl-1-dodecyl acetate, a component of the smaller tea tortrix (*Adoxophyes* sp.) sex pheromone, was synthesized in two ways via a common intermediate (36). The latter is obtained by the organocopper coupling reaction between bromide 16 or tosylate 14a and the respective complementary acetal components (ref. 8). More practical synthesis is based on the reaction of aldehyde 12 with the complementary ω -hydroxyalkyl phosphorane followed by hydrogenation of the diene intermediate 37.

Scheme 2

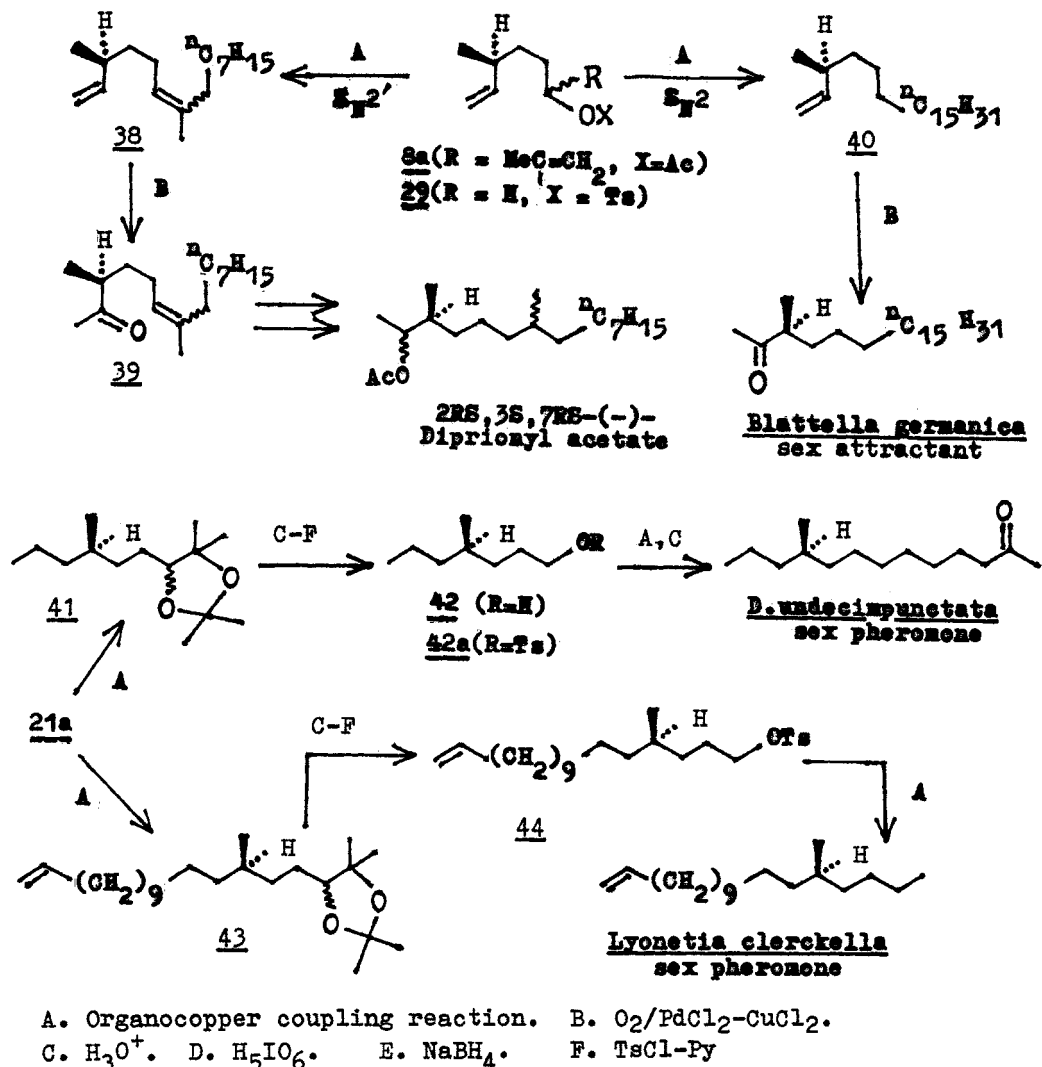


A. Organocopper coupling reaction; B. Wittig olefination

Although the Smidt-Wacker oxidation in the vicinity of a chiral centre may be configurationally unsafe, on two occasions we were fortunate to perform it without loss of optical activity. Thus, the 3RS,6S acetate 8a (derived from alcohol 8) was converted into diolefin 38 whose oxidation gave the dextrorotatory ketone 39. The latter in two steps afforded 2RS,3S,7RS-diprionyl acetate with the same sign of $[\alpha]_D$ as for the natural sex pheromone of pine sawflies (ref. 3). Similarly, tosylate 29 via olefin 40 was converted to S-3-methylheneicosan-2-one, a mimic of the *Blattella germanica* sex pheromone (ref. 9).

The sex pheromone of the southern corn rootworm (*Diabrotica undecimpunctata*), and that of the peach leafmining moth (*Lyonetia clerckella*) were synthesized from the bifunctional CBB 21a (ref. 10). In the first case it was cross-coupled with MeMgI to afford a C₁₁ block (41) which was converted into tosylate 42a via the corresponding alcohol (42). Precisely the same algorithm was followed in the second case to give intermediates 43 and 44 (Scheme 3).

Scheme 3



Pheromones with two or more chiral centres

R,R -Tribolure, the aggregation pheromone of *Tribolium* flour beetles, was obtained from the TGPP in several ways (refs. 4,11,12) outlined in Scheme 4. In all variants based on the organocopper cross-coupling 2-2.5 fold excess of the chiral Grignard reagent (from 15, 24, or 16) was required to obtain good yields in the key step. To avoid the waste of the chiral material, bromide 16 via the phosphonium salt 47 was converted into the corresponding phosphorane which was condensed with aldehyde 25 under neutral conditions. The resulting olefin 48 afforded upon hydrogenation the saturated intermediate 46 and hence R,R -tribolure in 16.7% overall yield (ref. 14).

The pheromone complex of the larger elm bark beetle (*Scolytus scolytus*) contains S,S -4-methyl-3-heptanol as one of the active ingredients while its $3R,4S$ -epimer, secreted in small amounts, acts as a weak synergist. Both were obtained from aldehyde 25, whose reaction with EtMgBr in accordance with Cram's rule gave, upon acetylation, the S,S -acetate 49 (threo) and its $3R,4S$ -counterpart 50 (erythro) in the ratio ca.7:3.

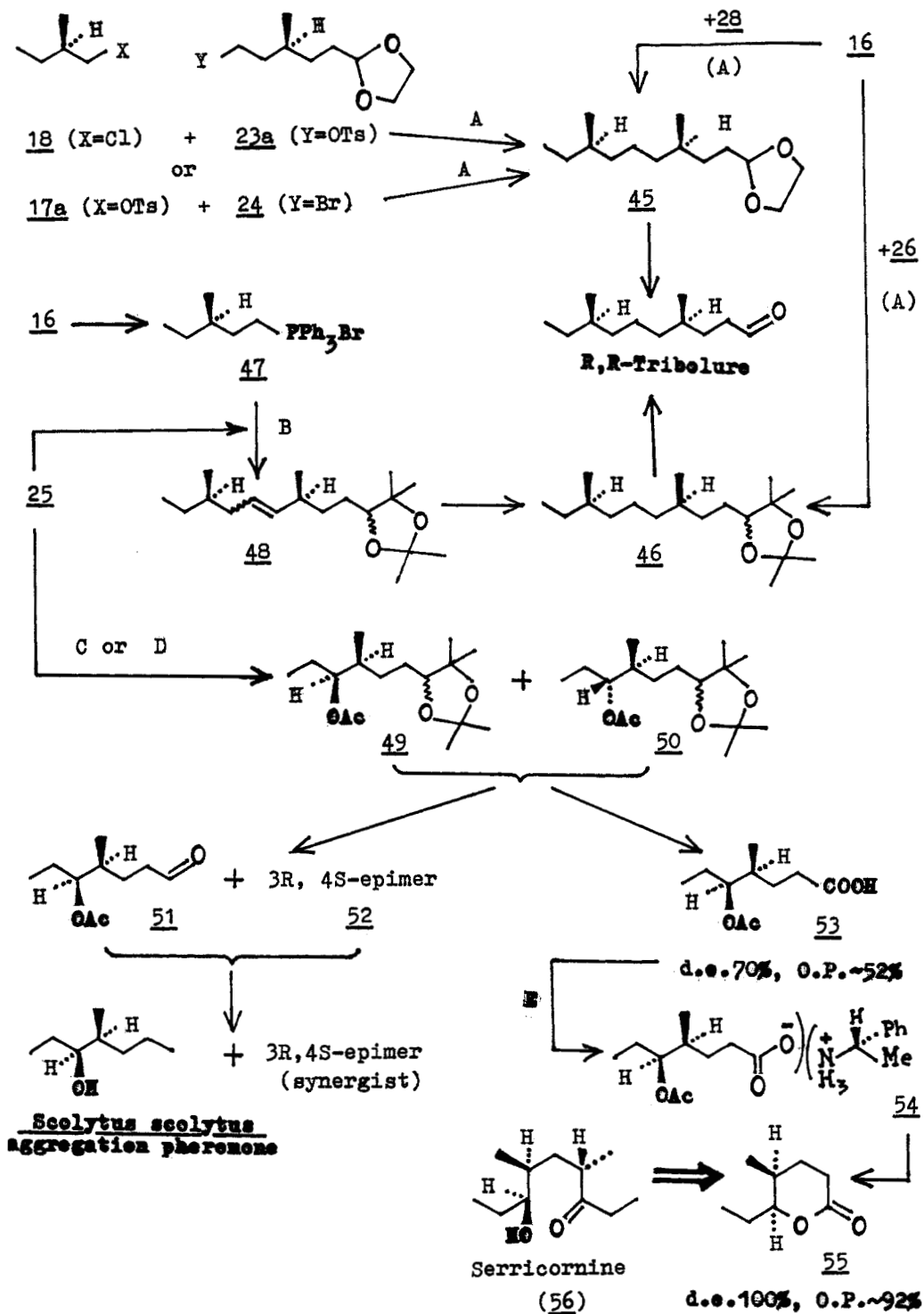
Hydrolysis of this mixture followed by periodate cleavage afforded the threo aldehyde 51 and its erythro epimer 52 in the same ratio.

The Wolff-Kishner reduction of these acetoxy aldehydes gave a mixture of the $3S,4S$ - and $3R,4S$ -alcohols in a ratio close to that found for *S.scolytus* (ref. 13) (Scheme 4).

Upgrading of optical purity

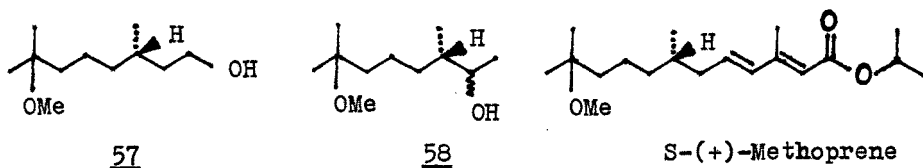
The values of $[\alpha]_D$, and the data of HPLC and $^1\text{H-NMR}$ spectra for the S -MTPA esters of alcohols 14,23, and 42, show that the O.P. values of our CBBs lay within 50±5%. That correlates well with the O.P. value of the original (+)- α -pinene. Can those inexpensive CBBs be used

Scheme 4



A. Organocopper coupling reaction. B. Wittig olefination.
 C. EtMgBr. D. EtTi(OPr-*i*)₃. E. S-PEA, crystallization.

to obtain products of higher enantiomeric purity? Their non-racemic nature makes this quite feasible. Thus, the acetoxy acid 53 (d.e. 70%, e.e. 52%), obtained from 49+50 (ref. 14), was treated with *S*-PEA to give a mixture of diastereomeric salts. Its repeated crystallization afforded diastereomerically pure salt 54, whose hydrolysis gave lactone 55 with d.e. 100% and e.e. 92% in 16% yield overall. Earlier, lactone 55 had been the penultimate intermediate in one of the syntheses of serricornine, the sex pheromone of the cigarette beetle (ref. 17), so our result is formally equivalent to a twelve-step synthesis of serricornine from *S*-1. *S*-Methoprene is known to display higher morphogenetic activity than its d,l-form. Starting from alkene 5 (O.P. 50%) we prepared in 29% yield a sample of *S*-methoprene with e.e. 67% (ref. 16). A mixture of *S*-methoxycitronellol (57) with 2*R*,3*S*-osyrol (58), obtained from 5 upon hydroboration-oxidation (57:58=94:6), was converted into a mixture of hemiphtalates and then treated with *S*-PEA to give a mixture of regio- and stereoisomeric salts. Two crystallizations from Et₂O-hexane provided a salt, from which chemically pure alcohol 57 with e.e. 67% was recovered and processed to *S*-methoprene.



CONCLUSION

Our examples show that the TGPP-derived CBBs can be successfully used to synthesize chiral molecules of higher optical purity if at an appropriate moment an optical resolution step is included in the synthetic sequence. The higher the optical purity of *S*-1 in the TGPP, the more efficient this procedure will be. Obviously, these arguments are equally valid for the laevorotatory TGPP, the use of which may offer further opportunities for the synthesis of chiral isoprenoids and propiogenins.

REFERENCES

- (a) F.Näf, R.Decorant, W.Giersch, G.Ohloff, *Helv.Chim.Acta* **64**, 1387-1397 (1981). (b) A.C. Barrett, R.A. Carr, S.V. Attwood, G. Richardson, N.D. Walsche, *J.Org.Chem.* **51**, 4840-4856 (1986). (c) R.E. Ireland, G.J. McGarvey, R.C. Anderson, R. Badoud, B. Fitzsimmons, S.Thaisrivong, *J.Am.Chem.Soc.* **102**, 6178-6180 (1980).
- GB 859568 (1961); *C.A.* **55**, 17507g (1961).
- Nguyen Cong Hao, M.V. Mavrov, E.P. Serebryakov, *Izvest.Akad.Nauk SSSR, Ser.Khim.* 1142-1146 (1988).
- SU 1284979 (1987); *C.A.* **106**, 213633c (1987).
- Nguyen Cong Hao, M.V. Mavrov, E.P. Serebryakov, *Izvest.Akad.Nauk SSSR, Ser.Khim.* 251-252 (1986).
- (a) Idem, *Ibid.* 903-906 (1987). (b) Idem, *Ibid.* 906-910 (1987).
- Idem, *Ibid.* 2080-2083 (1987).
- Idem, *Ibid.* 690-693 (1988).
- Idem, *Ibid.* 693-695 (1988).
- (a) Idem, *Ibid.* 2083-2085 (1987). (b) Idem, *Bioorg.Khim.* **14**, 250-252 (1988).
- Idem, *Zh.Org.Khim.* **23**, 1649-1653 (1987).
- Idem, *Bioorg.Khim.* **15**, 123-26 (1989).
- Idem, *Izvest.Akad.Nauk SSSR, Ser.Khim.* 1792-1795 (1987).
- Idem, *Ibid.* 1361-1364 (1989).
- Y. Takeda, Y. Kobayashi, F.Sato, *Chem.Lett.* 471-472 (1985).
- E.P. Serebryakov, G.M. Zhdankina, G.V. Kryshnal, M.V. Mavrov, Nguyen Cong Hao, *Izvest.Akad.Nauk SSSR, Ser.Khim.* (in press).