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# Stereochemistry of contiguous cyclopropane formation from cascade cyclization of a skipped dienyl homoallyl triflate

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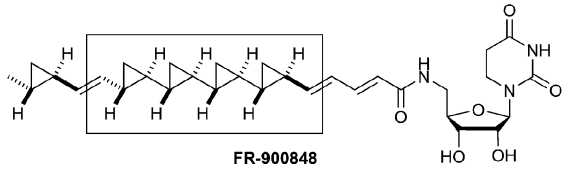
**Solvolysis of asymmetric homoallylic triflates bearing a terminal stannyl substituent gives disubstituted cyclopropanes and bicyclopropanes bearing differentiated termini in high enantiopurity.**

The rearrangement of a homoallyl cation to a cyclopropylcarbinyl cation is thought to play a role in the biogenesis of a variety of cyclopropane-containing natural products,[1] a hypothesis which previously led us to design successful biomimetic syntheses of eicosanoids such as the constanolactones.[2] The strategy underlying this approach to cyclopropane synthesis can be applied more broadly and would be particularly valuable if it could be extended to a set of contiguous cyclopropanes such as that present in the fungal metabolite FR-900848.[3]

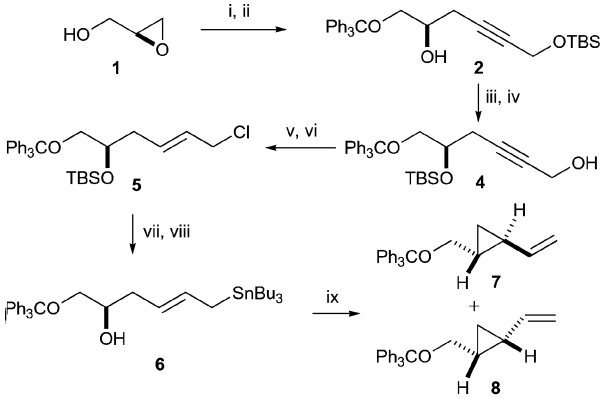



We have examined the rearrangement of homoallylic systems bearing a leaving group (triflate) at one terminus and a cation-stabilizing metal (tin) at the other to clarify the role of double bond geometry in the cyclization process as well as elucidate the absolute stereochemistry associated with this reaction. Related studies in a racemic series bearing a terminal silicon substituent have been published by Taylor.[4]

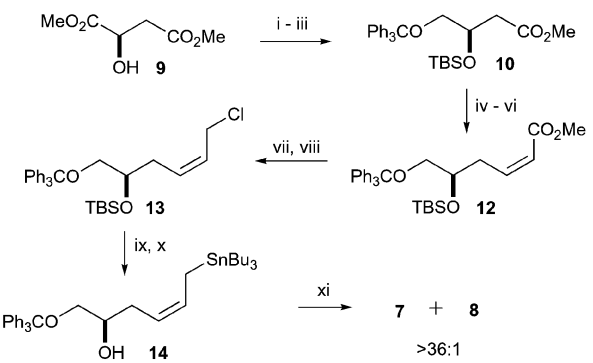
We first studied the reactivity of an enantiopure *trans*-homoallylic triflate bearing a tri-*n*-butylstannyl residue at the distal terminus. Synthesis of the requisite homoallylic alcohol began from (*S*)-(−)-glycidol (**1**) which was protected as its trityl ether before conversion to alkynol **2** with lithiated alkyne **3** (Scheme 1). Protection of the secondary alcohol followed by unmasking of the primary hydroxyl group gave **4** which was reduced with Red-Al to a *trans*-allylic alcohol. The derived allylic chloride **5** underwent displacement with lithio tri-*n*-butylstannane,[5] and subsequent cleavage of the silyl ether afforded **6**. Exposure of **6** to triflic anhydride in base at low temperature resulted in rapid solvolysis of the transient homoallylic triflate to produce a mixture of two cyclopropanes in quantitative yield. These cyclopropanes were readily identified by $^1$H NMR as *trans*- and *cis*-vinylcyclopropanes **7** and **8**, formed in the ratio 7.6 : 1 respectively. HPLC analysis on a stationary chiral phase showed **7** and **8** to be enantiomerically pure.

In order to study the effect of double bond geometry on the homoallyl-to-cyclopropylcarbinyl cyclization, the *cis*-isomer of **6** was synthesized from (*R*)-(+)-dimethyl malate (**9**), as shown in Scheme 2. Selective reduction of this diester,[6] masking of the resultant primary alcohol as its trityl ether, and protection of the remaining secondary alcohol led to **10**. This ester was converted to the corresponding aldehyde which was condensed with phosphonate **11**[7] to give *cis*-α,β-unsaturated ester **12**. Transformation of **12** to allylic chloride **13** and displacement with lithio tri-*n*-butylstannane[5] furnished *cis*-homoallylic alcohol **14**. Treatment of **14** with triflic anhydride under conditions similar to those used for **6** yielded *trans*-cyclopropane **7** as virtually the sole product (**7** : **8** > 36 : 1). A rationale for the improved stereoselectivity seen in the cyclization of **14** as compared with **6** must await further study.

The efficient cyclization of homoallylic alcohol **14** to cyclopropane **7** suggested an extension to a system containing a skipped diene, where a second contiguous cyclopropane could be formed in a cascade process. For this purpose, we prepared *cis*-3-(tri-*n*-butylstannyl)-2-propenol (**15**)[8] from propargyl alcohol and coupled this stannane in a Stille reaction with *trans*-allylic chloride **5** (Scheme 3). Conversion of the resulting alcohol to allylic chloride **16** was followed by displacement with lithio tri-*n*-butylstannane[5] and cleavage of the silyl ether to yield alcohol **17**. Treatment of **17** with triflic anhydride in collidine resulted in the quantitative formation of three enantiomerically pure, stereoisomeric bicyclopropanes in the ratio 3.7 : 1 : 1.




**Scheme 1** *Reagents and conditions*: i, $Ph_3CCl$, $Et_3N$, $CH_2Cl_2$, 92%; ii, $LiC{\equiv}CCH_2OTBS$ (**3**), THF, $BF_3{\cdot}OEt_2$, −78 °C, 93%; iii, TBSCl, imidazole, DMF; iv, TBAF, THF, 80% from **2**; v, Red-Al, $Et_2O$; vi, MsCl, LiCl, collidine, DMF, 0 °C → rt, 83% from **4**; vii, $LiSnBu_3$, THF, −78 °C, 93%; viii, TBAF, THF, 79%; ix, $Tf_2O$, collidine, $CH_2Cl_2$, $Et_3N$, −88 °C, 99%.




**Scheme 2** *Reagents and conditions*: i, $BH_3{\cdot}SMe_2$, $NaBH_4$ (cat), THF, 88%; ii, $Ph_3CCl$, $Et_3N$, $CH_2Cl_2$, 64%; iii, TBSCl, imidazole, DMF, 92%; iv, DIBALH, $CH_2Cl_2$, 0 °C, 94%; v, TPAP (cat), NMO, 4 Å mol. sieves, $CH_2Cl_2$, 78%; vi, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (**11**), KHMDS, 18-crown-6, THF, 89%; vii, DIBALH, $CH_2Cl_2$, 0 °C, 76%; viii, MsCl, LiCl, collidine, DMF, 0 °C → rt, 99%; ix, $LiSnBu_3$, THF, −78 °C, 93%; x, TBAF, THF, collidine, 0 °C → rt, 63%; xi, $Tf_2O$, collidine, $CH_2Cl_2$, $Et_3N$, −78 °C, 91%.

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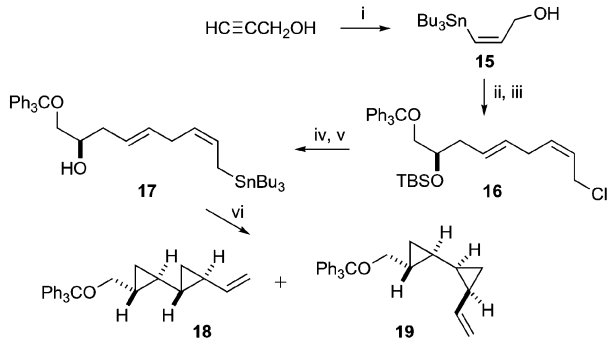
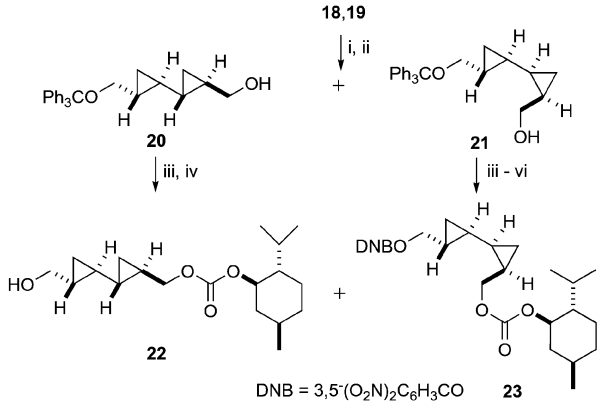


**Scheme 3** *Reagents and conditions*: i, $LiAlH_4$, THF; $Bu_3SnOTf$, 0 °C → rt, 83%; ii, **5**, $PdCl_2(MeCN)_2$, NMP; iii, MsCl, LiCl, collidine, DMF, 0 °C → rt; iv, $LiSnBu_3$, THF, −78 °C, 78% from **15**; v, TBAF, THF, $Et_3N$, 72%; vi, $Tf_2O$, collidine, $CH_2Cl_2$, $Et_3N$, −78 °C, 99%.

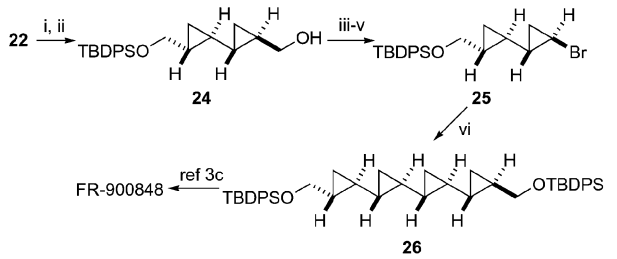


**Scheme 4** *Reagents and conditions*: i, $K_2OsO_4{\cdot}H_2O$, $NaIO_4$, THF–$H_2O$; ii, $NaBH_4$, THF–$H_2O$; iii, (−)-menthyl chloroformate, MeCN, pyridine; iv, $H_2$, $Pd(OH)_2$/C, EtOH, 45% (four steps); v, 3,5-dinitrobenzoyl chloride, pyridine, $CH_2Cl_2$; vi, $C_6H_5CO_2Na$, MeOH–$H_2O$, 8% (five steps).

In order to determine the configuration of the major isomer **18**, the mixture produced from **17** was oxidized with potassium osmate and sodium periodate and the resultant aldehydes were reduced to primary alcohols **20** and **21** (Scheme 4). These alcohols were reacted with (−)-menthyl chloroformate and the trityl group was removed by hydrogenolysis to give a mixture from which the major stereoisomer was separated by chromatography and crystallized. This compound was shown by X-ray crystallographic analysis† to possess the relative configuration of *trans*,*syn*,*trans*-bicyclopropane **22**, the absolute configuration being defined by the configuration of (−)-menthol.

One of the two minor stereoisomers was found to have the *trans*,*anti*,*cis* configuration of **21** by its transformation to the 3,5-dinitrobenzoate derivative **23** which also yielded to X-ray crystallographic analysis.† The bicyclopropanes from which **22** and **23** originate are therefore **18** and **19**, respectively, and our results confirm that in each case inversion took place at the hydroxyl-bearing carbon of **17** as the first cyclopropane was formed. Formation of the second cyclopropane, if it is in concert with the first, should lead to **18**, but the presence of **19** suggests the cascade process is partially interrupted at a monocyclopropylcarbinyl cation with consequent loss of stereocontrol in the second cyclization event. The third stereoisomeric bicyclopropane from **17** was also obtained in pure form as its 3,5-dinitrobenzoate and has been tentatively identified as the *trans*,*syn*,*cis* isomer.

The utility of this bicyclopropane synthesis was demonstrated by the conversion of **22** to an intermediate employed by Falck in his synthesis of FR-900848.[3c] Thus, protection of alcohol **22** was followed by reduction of the menthyl carbonate to yield alcohol **24**



**Scheme 5** *Reagents and conditions*: i, TBDPSCl, imidazole, DMAP, $CH_2Cl_2$, 93%; ii, DIBALH, $CH_2Cl_2$, −20 °C, 61%; iii, TPAP (cat), NMO, 4 Å mol. sieves, $CH_2Cl_2$; iv, $NaClO_2$, $KH_2PO_4$, $H_2O_2$, MeCN–$H_2O$; v, DCC, $BrCCl_3$, 2-mercaptopyridine-*N*-oxide, *hv*, 0 °C, 52% from **24**; vi, *t*-BuLi, CuI.$PBu_3$, $O_2$, −78 °C, 75% (ref. 3*c*).

(Scheme 5). Oxidation of **24** to the corresponding carboxylic acid and brominative decarboxylation under photolytic conditions afforded the bromobicyclopropane **25**. Falck has shown that copper catalyzed homocoupling of **25** yields a quatercyclopropane **26** which has been elaborated to FR-900848.[3c]

In summary, we have shown there is a pathway in the solvolytic displacement of homoallylic triflates which can be used in a cascade process to generate the *trans*,*syn*,*trans* configuration of a contiguous bicyclopropane. The method produces differentiated terminal functional groups, a feature which lends itself to the synthesis of polycyclopropane motifs in natural products such as FR-900848.

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## Notes and references

† Crystal data for **22** ($C_{19}H_{32}O_4$, $M$ = 324.45): $T$ = 100 K, monoclinic, unit cell dimensions $a$ = 9.2830(7), $b$ = 5.5489(5), $c$ = 18.4252(14) Å, $\beta$ = 90.844(6)°, $V$ = 948.99(13) Å$^3$, $P2_1$ (#4), $Z$ = 2, $\mu$ = 0.621 mm$^{-1}$. Rigaku/MSC Rapid, CuKα radiation: 6021 reflections measured in the range $4.76 < \theta/° < 59.99$, of which 2220 unique ($R_{int}$ = 0.0895). Final refinement of 219 parameters against this data set including 8 additional restraints yielded $R1$ = 0.0818 (all data), $wR2$ = 0.1972 (all data). For **23** ($C_{26}H_{34}N_2O_9$, $M$ = 518.55): $T$ = 100 K, orthorhombic, unit cell dimensions $a$ = 7.5080(3), $b$ = 8.6340(3), $c$ = 40.4790(15) Å, $V$ = 2624.01(17) Å$^3$, $P2_12_12_1$ (#19), $Z$ = 4, $\mu$ = 0.834 mm$^{-1}$. Rigaku/MSC Rapid, CuKα radiation: 27905 reflections measured in the range $2.18 < \theta/° < 71.31$, of which 3925 unique ($R_{int}$ = 0.015). Final refinement of 337 parameters against this data set yielded $R1$ = 0.0483 (all data), $wR2$ = 0.1190 (all data). CCDC 249269–242970. See http://www.rsc.org/suppdata/cc/b4/b412811g/ for crystallographic data in .cif or other electronic format.


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