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Stereospecific Intramolecular Michael Addition to (–)-Carvone Based on Temporary Sulfur Connection

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Abstract

An acetic acid residue (CH_2CO_2Me) was stereoselectively attached to (–)-carvone (**7**) to give (1*R*,2*S*,5*R*)-(5-isopropenyl-2-methyl-3-oxocyclohexyl)acetic acid methyl ester (**21**) in a process involving the following stages: i) addition of $ClSCH_2CO_2Me$ to the isopropenyl group of **7** to give, after oxidation, [1-chloro-2(*RS*)-(1(*R*),4-methyl-5-oxocyclohex-3-enyl)propane-2-sulfonyl]acetic acid methyl ester (**18**); ii) intramolecular Michael addition of **18** to afford (1*S*,2*S*,4(*RS*),5*R*,8*S*)-4-chloromethyl-4,8-dimethyl-3,3,7-trioxo-3-thiabicyclo [3.3.1]nonane-2-carboxylic acid methyl ester (**20**); iii) disconnection of the acetic acid moiety by a tandem reductive elimination involving sulfur extrusion and restoration of the isopropenyl group (**20** → **21**).

Keywords: elimination reactions / enantioselection / Michael reactions / terpenes and terpenoids

Temporary tethering of two reactants for inducing intramolecular *in lieu* of intermolecular reactions constitutes a useful strategy for controlling regio- and stereoselectivity in carbon-carbon bond formation. Synthetic methods based on temporary silicon connection [1] have been comprehensively [2-4] reviewed. These methods usually involve the use of a hydroxyl group of one reactant as an anchor to which a second reactant is linked through a silicon connector. Accordingly, the process of connection and disconnection involves reactions in which silicon-oxygen and silicon-carbon bonds are selectively formed and cleaved. Due to the different chemical properties of carbon-sulfur bonds in various oxidation states (C-S; C-SO; $C\text{-}SO_2$) as compared to carbon-silicon bonds, temporary sulfur connection [5-14] emerges as a complementary methodology to the temporary silicon connection.

In our recent stereoselective synthesis of (±)-α-kainic acid [6,7] and enantioselective total synthesis [8] of (–)-α-kainic acid, we introduced a method for the regio- and stereoselective attachment of an acetic acid residue to a pyrrolidine derivative. It is based on the strategy delineated in Scheme 1 (path a) which involves three stages: i) anchoring stage in which an acetic acid residue is attached through a sulfur linker Y to an isopropenyl group; ii) intramolecular cyclization in which an acetic acid residue is regio- and stereoselectively attached to a cyclic system through substitution of a leaving group X; and iii) disconnection of the acetic acid residue from its anchor through sulfur extrusion and restoration of the isopropenyl group. Applying the same strategy of temporary sulfur connection, but varying the methodology, we report herein on the enantioselective synthesis of all *cis*- trisubstituted cyclohexanone **21**.

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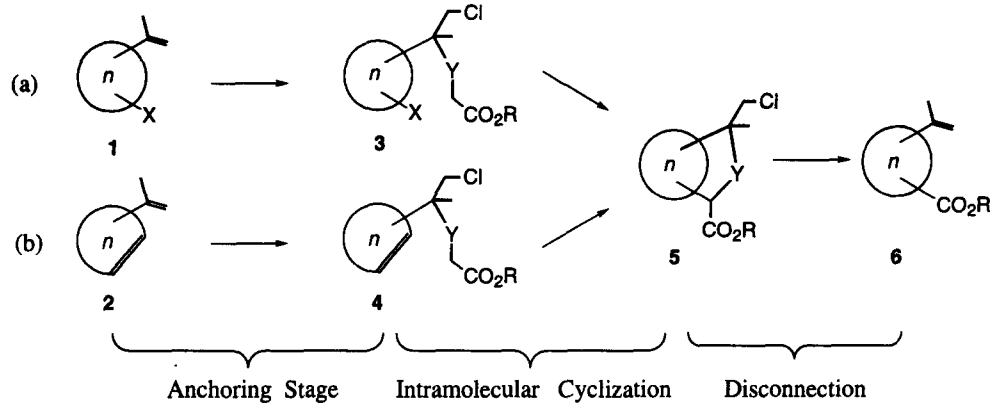
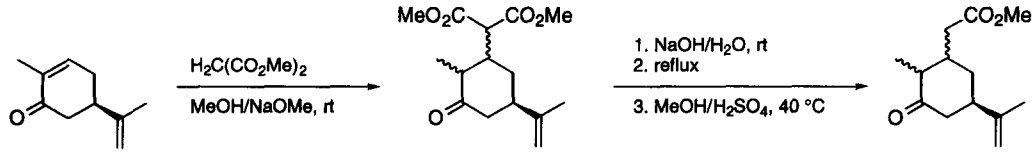
A Strategy for Temporary Sulfur Connection



X = leaving group
Y = sulfur linker; S, SO, or SO_2
n = 5 or 6-membered rings

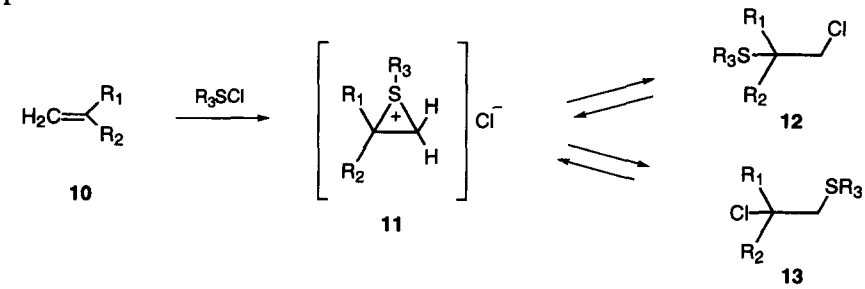
Scheme 1

As expected, a simple base-induced intermolecular Michael addition of dimethyl malonate to (–)-carvone (**7**) afforded adducts **8**, and after subsequent partial decarboxylation four trisubstituted diastereomeric cyclohexanones **9**. In this reaction the all *cis*-isomer of **9**, namely compound **21** (*cf.* Scheme 3), was obtained in less than 5% overall yield (Scheme 2). It was reasoned that application of temporary sulfur connection as outlined in Scheme 1 (path b) may be used for the enantiospecific preparation of **21** through an intramolecular Michael addition.



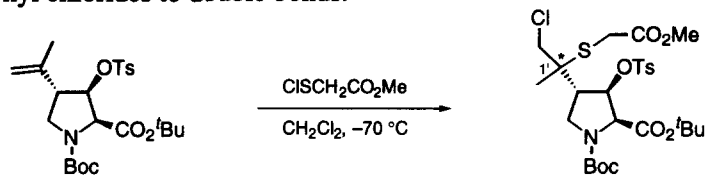
Scheme 2

A straightforward method for tethering carbon appendages through a sulfur connector involves addition of sulfenyl chlorides to double bonds. Electrophilic addition of sulfenyl chlorides to a non-activated double bond, which proceeds *via* intermediate episulfonium ion **11**, was used [15-17] for the synthesis of β-chloroalkyl sulfides of type **12** as well as their regioisomers of type **13** (Scheme 3). Regiocontrol thus constitutes a major challenge in synthetic application of this reaction.



Scheme 3

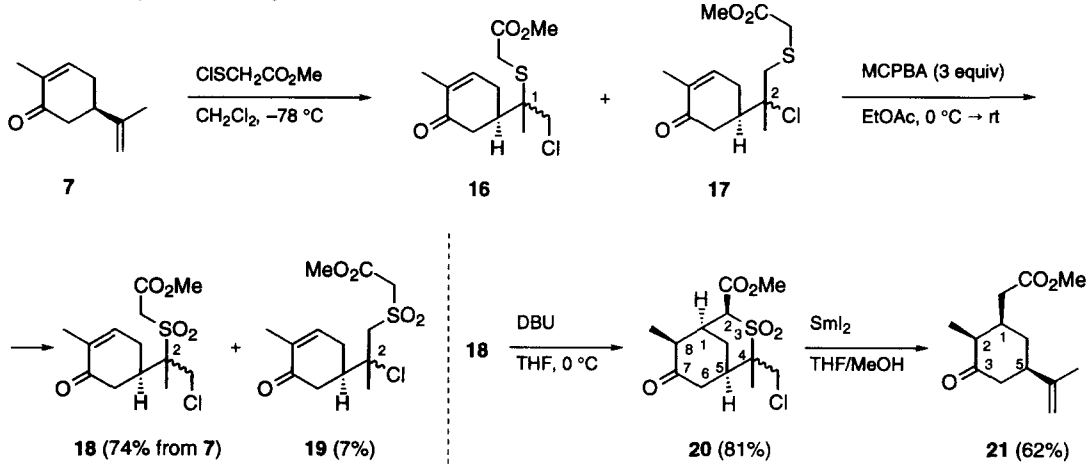
In the context of the synthesis [6-8] of (±)-α- and (–)-α-kainic acid, we found that addition of $ClSCH_2CO_2Me$ to the isopropenyl group of tosyloxy derivative **14** (Scheme 4) affords regio- and stereoselectively adduct **15**. This very high selectivity is unusual for addition reactions of sulfenyl chlorides to double bonds.



14 **15** (81%)

Scheme 4

Attempts to prepare β-chloroalkyl sulfide **16** from (–)-carvone (**7**) (Scheme 5), under the conditions reported [7] for the synthesis of adduct **15** from isopropenylproline derivative **14**, afforded only β-chloroalkyl sulfides **17**. However when $ClSCH_2CO_2Me$ [18] was added to (–)-carvone (**7**) at –78 °C, a mixture of regioisomers **16** and **17** was obtained (Scheme 5). The ^1H NMR of the product mixture showed that the major adduct was the β-chloroalkyl sulfide **16** (epimers at 1-C) but exact ratio of regioisomers could not be determined because the kinetic product **16** is extremely prone to isomerization to the more stable isomer **17**.[1,2] Flash-chromatography on silica gel of the mixture of β-chloroalkyl sulfides **16** and **17** gave β-chloroalkyl sulfide **17** as only product. In order to hamper the rearrangement of sulfide **16** into sulfide **17** (*cf.* Scheme 3), the crude product was immediately oxidized with an excess of MCPBA to β-chloroalkyl sulfones **18**.[3]



7 **16** **17** **18** (74% from **7**) **19** (7%) **18** **20** (81%) **21** (62%)

Scheme 5

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(1) All new compounds were fully characterized by detailed NMR analysis including 1D (^1H, ^{13}C/DEPT) and 2D-NMR spectra ($^1H/^1H$ COSY, $^1H/^{13}C$ HMQC). The target compound **21** was additionally characterized by CI HRMS.

(2) A similar process [19] was reported. Selected spectral data for compound **17**: ^1H NMR (two isomers, 250 MHz, $CDCl_3$): δ 1.67, 1.675 (2 x s, total 3H, $CH_3C(2)Cl$); 1.81 (m, 3H); 2.39-2.74 (m, 5H); 3.15 (d, J = 12.9 Hz), 3.17 (s), 3.24 (d, J = 12.9 Hz), 3.33 (s), total 4H; 3.78 (s, 3H); 6.77 (m, 1H).
Monitoring by NMR showed that a mixture of **16** (77%, ^1H NMR: δ 1.41 (s, 3H, $CH_3C(1)CH_2Cl$)) and **17** (23%, ^1H NMR: δ 1.67, 1.675 (2 x s, total 3H, $CH_3C(2)Cl$)) changed on standing at room temperature for *ca.* 12 hours to 47% : 53 % (**16** : **17**).

(3) *[1-Chloro-2(RS)-(1(R),4-methyl-5-oxocyclohex-3-enyl)propane-2-sulfonyl]acetic acid methyl ester* **18**: ^1H NMR (two isomers, 400 MHz, $CDCl_3$): δ 1.50, 1.52 (2 x s, 3H); 1.79 (br m, 3H); 2.37-2.75 (m, 4H); 2.81-2.97 (m, 1H); 3.78-4.31 (m, 4H); 6.77 (m, 1H). ^{13}C NMR (two isomers, 400 MHz, $CDCl_3$): δ 15.33, 15.38; 15.4, 16.0; 27.4, 27.6; 36.9, 37.4; 39.0, 39.7; 45.8, 45.9; 53.49, 53.53; 57.6, 57.8; 70.4; 135.5, 135.7; 143.3, 144.2; 162.3, 162.4.

Base-induced intramolecular Michael addition of β-chloroalkyl sulfones **18** (DBU/THF, 0 °C, 2 h, monitored by TLC) afforded 3-thiabicyclo[3.3.1]nonanes **20**.[4] The particular geometry of the bicyclo[3.3.1]nonane system forces the methyl group at 8-C and carbomethoxy group at 2-C into equatorial orientation, thus three new stereogenic centers (1*S*,2*S*,8*S*) were stereospecifically formed in one step. The all *cis*- trisubstituted cyclohexanone **21**[5] was obtained from bicyclic β-chloroalkyl sulfones **20** by a samarium(II) iodide-mediated tandem reductive elimination [7] in which the acetic acid moiety is disconnected with concomitant re-establishment of the original isopropenyl anchor.

In conclusion, the "temporary sulfur connection" strategy was employed for inducing an intramolecular Michael addition which allowed the enantiospecific conversion of (–)-carvone (**7**) into all *cis*- trisubstituted cyclohexanone **21** (37% overall yield).

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(4) 1,2-*Cis* configuration assignments for the two epimers **20** were corroborated on the ground of spin coupling constants $J_{H^1{}_eH^{2a}}$. The ^{1}H NMR spectra of the two 4-C epimers **20** exhibited the following relevant signals: the less polar isomer at 2-C**H** δ 4.19 with $J_{H^1{}_eH^{2a}} < 1$ Hz and the more polar isomer at 2-C**H** δ 4.12 with $J_{H^1{}_eH^{2a}} < 1$ Hz).

(5) *(1R,2S,5R)-(5-Isopropenyl-2-methyl-3-oxocyclohexyl)acetic acid methyl ester* **21**: IR (neat): ν 2970, 2951, 1737, 1711, 1437, 1378, 1258, 1173 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ 0.67 (d, *J* = 7.3 Hz, 3H); 1.12 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1H); 1.41 (m, 1H); 1.43 (br s, 3H); 1.91 (d, *J* = 7.3 Hz, 2H); 1.99 (m, 1H,); 2.10 (dd, *J* = 13.4, 13.4 Hz, 1H); 2.21 (m, 2H); 2.50 (dq, *J* = 7.3, 4.7 Hz, 1H); 3.29 (s, 3H); 4.57 (m, 1H); 4.65 (dq, *J* = 1.4, 1.4 Hz, 1H). ^{13}C NMR (400 MHz, C_6D_6): δ 10.9; 20.2; 30.9; 36.7; 37.3; 42.0; 44.3; 47.5; 51.1; 109.9; 147.4; 171.7; 211.0. HRMS (CI) *m/z* (r.i.): 225 (MH^+, 100), 193 (M^+ - OMe, 18), 151 (M^+ - CO_2Me, 7) (Found (MH^+), 225.1460. $C_{13}H_{21}O_3$ requires (MH^+), 225.1491).

To corroborate the stereochemical assignments of compound **21**, it was partially epimerized, by boiling with DBU in THF, to *(1R,2R,5R)-(5-Isopropenyl-2-methyl-3-oxocyclohexyl)acetic acid methyl ester* **22**: ^{1}H NMR (400 MHz, C_6D_6): δ 1.03 (d, *J* = 6.1 Hz, 3H); 1.16 (ddd, *J* = 13.0, 11.8, 11.8 Hz, 1H); 1.43 (s, 3H); 1.67 (dq, *J* = 12.6, 6.1 Hz, 1H); 1.68 (m, 1H); 1.79 (ddd, *J* = 13.0, 5.4, 3.0 Hz, 1H); 1.86 (ddd, *J* = 12.7, 12.7, 0.6 Hz, 1H); 1.91 (dd, *J* = 15.4, 8.0 Hz, 1H); 2.00 (m, 1H); 2.21 (dd, *J* = 15.4, 3.6 Hz, 1H); 2.39 (ddd, *J* = 12.6, 3.4, 2.3 Hz, 1H); 3.30 (s, 3H); 4.57 (m, 1H,); 4.65 (dq, *J* = 1.5 Hz, 1.5 Hz, 1H). ^{13}C NMR (400 MHz, C_6D_6): δ 11.8; 20.1; 37.1; 38.9; 41.3; 44.6; 46.4; 48.6; 51.0; 109.8; 147.5; 172.0; 208.5. 1,2-*Cis* and 1,2-*trans* configuration assignments for compounds **21** and **22** derived from spin coupling constants of the 2-C and 1-C protons: $J_{H^1{}_aH^{2e}}$ (*cis*) < $J_{H^1{}_aH^{2a}}$ (*trans*). 1,2-*Cis* isomer **21** and 1,2-*trans* isomer **22** exhibited upon irradiation of the 2-CCH_3 groups the following relevant signals: (400 MHz, C_6D_6), δ 2.50 (d, $J_{H^1{}_aH^{2e}}$ = 4.7 Hz, 2-C**H**) for **21** and (400 MHz, $CDCl_3$), δ 2.23 (d, $J_{H^1{}_aH^{2a}}$ = 12.6 Hz, 2-C**H**) for **22**.