

# **Stereocontrolled Synthesis of Trisubstituted Cyclopropanes: Expedient, Atom Economical, Asymmetric Syntheses of (+)- Bicifadine and DOV21947**

Feng Xu,\* Jerry Murry, Bryon Simmons, Edward Corley, Kenneth Fitch,  
Sandor Karady, David Tschaen

Department of Process Research, Merck Research Laboratories, Rahway, NJ 07065, USA

*E-mail: feng\_xu@merck.com*

## ***Supporting Information***

### Table of Contents

1. Single-stage through processes for the preparation of (+) Bicifadine and DOV21947 .....	S2
2. Table S1. Factors affecting the <i>cis/trans</i> ratio of cyclopropanation products .....	S5
3. Table S2. Substituent's effects on cyclopropanation .....	S6
4. Determination of ee% of the cyclopropanation products .....	S7
5. Alternative synthesis via lactone intermediate .....	S9
6. Unexpected reactivity of the <i>trans</i> chloride <b>12</b> .....	S9
7. Kinetic observations of the chlorination of <b>2</b> and <b>11</b> .....	S10
8. Cyclopropanation through tosylate <b>9</b> .....	S11

## 1. Single-stage through processes for the preparation of (+) Bicifadine and DOV21947

**General.** Unless otherwise noted, all reactions were conducted under N<sub>2</sub> atmosphere using standard air-free manipulation techniques. Solvents were purchased from Fisher Scientific Company and used without further purification. Commercial reagents were purchased either from Aldrich or Bayer and used without further purification. S-(+)-epichlorohydrin (98 ee%) can be purchased at bulk price of \$115/kg from Rhodia. High performance liquid chromatography (HPLC) analysis was performed using Agilent Technology 1100 series instrument with ACE 5 C18 (240 x 4.6 mm I.D., 5  $\mu$ m particle size) column. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were measured on Bruker Avance-400 instrument (400 MHz). Carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were measured on Bruker Avance-400 instrument (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS).

**(1R,5S)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane (DOV21947, 1b).** To a solution of 3,4-dichlorophenylacetonitrile (3.50 kg) and S-(+)-epichlorohydrin (2.22 kg) in THF (18.5L) at -15 °C under atmosphere of N<sub>2</sub> was added NaHMDS (16.5 L, 2M in THF) dropwise over 3 h. The reaction mixture was stirred for additional 3 h at -15 °C, then, overnight at -5 °C. BH<sub>3</sub>-Me<sub>2</sub>S (neat, 10M, 4.4 L) was added over 2 h. The reaction mixture was then gradually warmed to 40 °C over 3 h. After aging 1.5 h at 40 °C, the reaction mixture was cooled to 20-25 °C and slowly quenched into a 2N HCl solution (27.7 L). The quenched mixture was then stirred for 1 h at 40 °C. Conc. NH<sub>4</sub>OH (6.3 L) was added and the aqueous layer was discarded. *i*-PrOAc (18.5 L) and 5% dibasic sodium phosphate (18.5 L) were charged. The organic phase was then washed with saturated brine (18.5 L), azeotropically dried and solvent-switched to *i*-PrOAc (ca. 24.5 L) in vacuum.

The above crude amino alcohol solution in *i*-PrOAc was slowly subsurface-added to a solution of SOCl<sub>2</sub> (1.61 L) in *i*-PrOAc (17.5 L) at ambient temperature over 2 h. After aging additional 1-5 h, 5.0 N NaOH (16.4 L) was added over 1 h while the batch temperature was maintained at <30 °C with external cooling. The two-phase reaction mixture was stirred for 1 h at ambient temperature to allow pH to stabilize (usually to 8.5-9.0) with NaOH pH titration. The organic phase was washed with 40% aqueous *i*-PrOH (21 L) followed by water (10.5 L). Conc. HCl (1.69 L) was added. The aqueous *i*-PrOAc was azeotropically concentrated in vacuum to ca. 24.5 L. Methylcyclohexane (17.5 L) was added dropwise over 2 h. The wet cake was displacement-washed with 7 L of 40% methylcyclohexan/*i*-PrOAc followed by a slurry wash (7 L, *i*-PrOAc) and a displacement wash (7 L, *i*-PrOAc). Typical isolated yield: 57-60% corrected with wt% (87-99.5%, based on HCl salt **1b**). The variation of the wt% is due to the isolated crystal form composition (hemihydrate vs. anhydrous) and the amount of *trans* chloride HCl salt **12b** in the isolated solid, which can be varied between 9-0.2 A% depending on the

crystallization condition as well as the crude reaction impurity profile. However, 10A% of **12b** in a crude final product can be easily rejected to <0.14A% after one recrystallization.

**Recrystallization to prepare the hemihydrate HCl salt of **1b**.** The above DOV21947 HCl salt (5.0 kg) was dissolved in *i*-PrOH (14.25 L) and water (1.2 L) at 55 °C. Seeds (50 g) were added at 48-50 °C. The batch was allowed to cool to ambient temperature (20 °C) over 2-4 h. MeOBu-*t* (37 L) was added dropwise over 2 h. After aging 1 h at 20 °C, the batch was filtered. The wet cake was displacement-washed with 10 L of 30% *i*-PrOH in MTBE followed by 2x7.5 L 10% *i*-PrOH in MeOBu-*t* (slurry wash, then displacement wash). The wet cake was suction dried under N<sub>2</sub> (10 – 50% relative humidity) at ambient temperature to give the hemihydrate HCl salt in >99.8 A% and 100 ee%. Typical yield: 92%.

**DOV21947 hemihydrate HCl salt:** <sup>1</sup>H-NMR (400 MHz, *d*<sub>4</sub>-MeOH): δ 7.52 (d, *J* = 2.2 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.26 (dd, *J* = 2.1, 8.4 Hz, 1 H), 3.78 (d, *J* = 11.4 Hz, 1 H), 3.69 (dd, *J* = 3.9, 11.3 Hz, 1 H), 3.62 (dd, *J* = 1.4, 11.3 Hz, 1 H), 3.53 (d, *J* = 11.4 Hz, 1 H), 2.21 (m, 1 H), 1.29 (t, *J* = 7.5 Hz, 1 H), 1.23 (dd, *J* = 4.9, 6.5 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, *d*<sub>4</sub>-MeOH): δ 141.0, 133.7, 132.2, 132.0, 130.6, 128.4, 51.7, 49.1, 31.8, 24.9, 16.5. Anal. Calcd for C<sub>11</sub>H<sub>13</sub>Cl<sub>3</sub>NO<sub>0.5</sub>: C, 48.29; H, 4.79; N, 5.12; Cl, 38.88. Found: C, 48.35; H, 4.87; N, 5.07; 38.55.

**[(1S,2R)-2-(aminomethyl)-2-(3,4-dichlorophenyl)cyclopropyl]methanol (2b):** Crystalline free base **2b** can be isolated for characterization. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.50 (d, *J* = 2.1 Hz, 1 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 7.24 (dd, *J* = 2.1, 8.2 Hz, 1 H), 4.12 (dd, *J* = 5.4, 12.3 Hz, 1 H), 3.44 (d, *J* = 12.8 Hz, 1 H), 3.34 (dd, *J* = 11.0, 12.3 Hz, 1 H), 2.80 (s, br, 3 H), 2.60 (d, *J* = 12.8 Hz, 1 H), 1.72 (m, 1 H), 0.95 (dd, *J* = 4.9, 8.7 Hz, 1 H), 0.78 (t, *J* = 5.2 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 144.6, 132.5, 131.5, 130.9, 130.5, 129.0, 63.4, 46.6, 31.4, 25.5, 18.5. Anal. Calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub>: C, 53.68; H, 5.32; N, 5.69; Cl, 28.81. Found: C, 53.55; H, 5.20; N, 5.54; Cl, 28.54.

**[(1S,2S)-2-(aminomethyl)-2-(3,4-dichlorophenyl)cyclopropyl]methanol (11b):** The minor *trans* amino alcohol **11b** was isolated as its free base by preparative HPLC for characterization. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.47 (d, *J* = 1.9 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.24 (dd, *J* = 1.9, 8.2 Hz, 1 H), 3.40 (dd, *J* = 6.1, 11.2 Hz, 1 H), 3.14 (dd, *J* = 8.1, 11.2 Hz, 1 H), 2.98 (d, *J* = 13.3 Hz, 1 H), 2.55 (d, *J* = 11.3 Hz, 1 H), 1.96 (s, br, 3 H), 1.37 (m, 1 H), 0.94 (dd, *J* = 5.1, 8.7 Hz, 1 H), 0.77 (t, *J* = 5.1 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 140.4, 132.7, 132.6, 131.3, 130.6, 130.1, 63.4, 52.6, 34.3, 25.5, 14.1.

**(1R,5S)-1-(4-methylphenyl)-3-azabicyclo[3.1.0]hexane [(+)-Bicifadine, **1a**].** To a solution of 4-methylphenylacetonitrile (100 g) and *S*-(+)-epichlorohydrin (86.4 g) in MeOBu-*t* (800 mL) between -25 to -30 °C under atmosphere of N<sub>2</sub> was added LiHMDS (971 mL, 1M in hexane) dropwise over 2 h. After aging additional 2 h at -30 °C, the reaction mixture was quenched into 5N HCl (448 mL) while the temperature was

maintained below 20 °C. After phase separation, the organic phase was washed with water (200 mL), azeptropically dried and solvent-switched to (MeOCH<sub>2</sub>)<sub>2</sub> (ca. 1 L) in vacuum.

To the above solution of the crude chlorohydrin in (MeOCH<sub>2</sub>)<sub>2</sub> at -15 °C was added NaHMDS solution (747 mL, 2M in THF) dropwise over 2 h. The reaction mixture was stirred for additional 1 h between -15 to -20 °C. Then, BH<sub>3</sub>-Me<sub>2</sub>S (neat, 10M, 224 mL) was added dropwise over 1-2 h while the internal temperature was kept below 10 °C. The reaction mixture was then gradually warmed to 40 °C over 2 h and stirred for additional 3 h at 40 °C. The reaction mixture was cooled to 20-25 °C and slowly quenched into a 4N HCl (934 mL) solution. The mixture was then aged for 1 h at 40 °C. Ammonium hydroxide (401 mL) and *i*-PrOAc (500mL) was added. The aqueous phase was back extracted with *i*-PrOAc (400 mL). The combined organic phase was washed with water (100 ml x 2), azeptropically dried and solvent-switched to *i*-PrOAc in vacuum (ca. 800 mL).

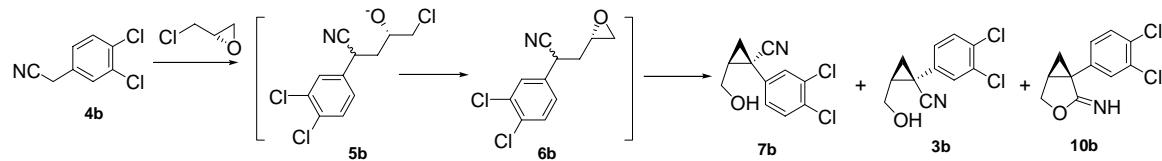
The above crude amino alcohol solution in *i*-PrOAc was slowly subsurface-added to a solution of SOCl<sub>2</sub> (66.5 mL) in *i*-PrOAc (450 mL) at ambient temperature over 2 h. After aging additional 1-3 h, 5.0 N NaOH (674 mL) was added over 1 h while the batch temperature was maintained at <30 °C with external cooling. The two-phase reaction mixture was stirred for 1 h at ambient temperature to allow pH to stabilize (usually to 8.5-9.0) with NaOH pH titration. The organic phase was washed with water (2 x 100 mL). Conc. HCl (68.5 mL) was added to the organic phases while the internal temperature was kept <30 °C. The aqueous *i*-PrOAc was azeotropically concentrated in vacuum to a final volume of ca. 500 mL. Methylcyclohexane (350 mL) was added slowly over 2 h. The wet cake was displacement washed with 150 mL of 45% methylcyclohexan/*i*-PrOAc followed by a slurry wash (150 mL, *i*-PrOAc) and a displacement wash (150 mL, *i*-PrOAc). Typical isolated yield: 65% over 4 steps. >99 ee%

**Recrystallization of (+)-Bicifadine.** (+)Bicifadine HCl salt (100 g) was dissolved in a solution of *i*-PrOH (285 mL) and water (15 mL) at 75 °C. Seeds (1 g) was added and the batch was allowed to cool to ambient temperature over 2-4 h. MeOBu-*t* (700 mL) was then added dropwise over 2 h. After 1 h agitation at 20 °C, the slurry was filtered. The wet cake was displacement washed with 150 mL of 30% *i*-PrOH in MeOBu-*t* followed by 2x150 mL 10% *i*-PrOH in MeOBu-*t* (slurry wash, then displacement wash). The (+)-Bicifadine HCl salt (>99.8 A% and >99 ee%) was suction dried under N<sub>2</sub> at ambient temperature. Typical yield: 95%.

**(+)-Bicifadine HCl salt:** <sup>1</sup>H-NMR (400 MHz, *d*<sub>4</sub>-MeOH): δ 7.17 (m, 4 H), 3.73 (d, *J* = 11.4 Hz, 1 H), 3.66 (dd, *J* = 3.8, 11.4 Hz, 1 H), 3.58 (d, *J* = 11.4 Hz, 1 H), 3.51 (d, *J* = 11.4 Hz, 1 H), 2.31 (s, 3 H), 2.10 (m, 1 H), 1.22 (t, *J* = 7.5 Hz, 1 H), 1.12 (t, *J* = 5.4 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, *d*<sub>4</sub>-MeOH): δ 138.3, 136.8, 130.6, 128.3, 52.3, 49.3, 32.3, 24.2, 21.2, 16.0. Anal. Calcd for C<sub>12</sub>H<sub>16</sub>ClN: C, 68.73; H, 7.69; N, 6.68. Found: C, 68.52; H, 7.69; N, 6.64.

**[(1S,2R)-2-(aminomethyl)-2-(4-methylphenyl)cyclopropyl]methanol fumaric salt (2a):** **2a** can be isolated as its fumaric salt for characterization.  $^1\text{H-NMR}$  (400 MHz,  $d_4$ -MeOH):  $\delta$  7.32 (d,  $J$  = 7.8 Hz, 2 H), 7.19 (d,  $J$  = 7.8 Hz, 2 H), 6.68 (s, 2 H), 4.18 (dd,  $J$  = 5.7, 12.0 Hz, 1 H), 3.40 (dd,  $J$  = 10.3, 12.0 Hz, 1 H), 3.39 (d,  $J$  = 13.6 Hz, 1 H), 3.22 (d,  $J$  = 13.6 Hz, 1 H), 2.33 (s, 3 H), 1.68 (m, 1 H), 1.15 (dd,  $J$  = 8.8, 5.2 Hz, 1 H), 0.97 (t,  $J$  = 5.4 Hz, 1 H).  $^{13}\text{C-NMR}$  (100 MHz,  $d_4$ -MeOH):  $\delta$  171.6, 139.9, 138.8, 136.4, 130.9, 130.6, 62.8, 46.5, 29.4, 27.4, 21.2, 18.3. Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{NO}_5$ : C, 62.53; H, 6.89; N, 4.56. Found: C, 62.36; H, 6.88; N, 4.47.

**2. Table S1. Factors affecting the *cis/trans* ratio of cyclopropanation products<sup>a</sup>**



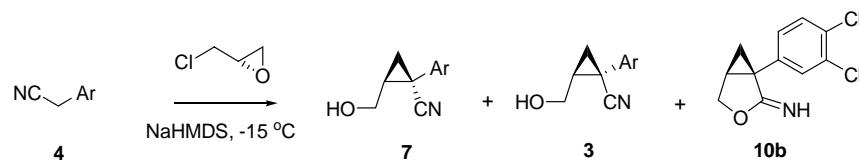
Bases	Additives	Temp. (°C)	Solvents	<i>cis:trans</i> <sup>b</sup>
NaHMDS		-60 -> rt	THF	83:17
NaHMDS		-40 to -35	THF	87:13
<b>NaHMDS</b>		<b>-20</b>	<b>THF</b>	<b>85:15</b>
NaHMDS	18-crown-6	-20	THF	85:15
NaHMDS		-15	MeOBu- <i>t</i> /THF	75:25
NaHMDS		20	THF	79:21
NaHMDS		20	Cyclohexane/THF	70:30
NaHMDS	7 equiv LiCl	20	THF	78:22
NaHMDS	Ti(OEt) <sub>4</sub>	20	THF	79:21
NaHMDS	Sm(OTf) <sub>3</sub>	20	THF	77:23
NaHMDS		-60 to rt	MeOCH <sub>2</sub> CH <sub>2</sub> OMe	83:17
KHMDS		20	PhMe	69:31
KHMDS	Sc(OTf) <sub>3</sub>	20	PhMe	60:40
KHMDS	Y(OTf) <sub>3</sub>	20	PhMe	52:48
KHMDS		20	Me <sub>2</sub> NAc	85:15 (racemic)
DBU		20 – 40	THF	No reaction
KOBu- <i>t</i>		-20 to -10	THF	78:22
NaH		-15	THF	81:19
NaNH <sub>2</sub>		0	C <sub>6</sub> H <sub>6</sub>	80:20

- a. For a typical experimental procedure: To a solution of 3,4-dichlorophenylacetonitrile (1 equiv) and *S*-(+)-epichlorohydrin (1.2 equiv) in the presence/absence of an additive in a solvent (10 mL/1 g **4b**) at the temperature as specified in Table S1 under atmosphere of N<sub>2</sub> was added a solution of a base (1.3 equiv, in the same reaction

solvent) dropwise over 3 h. The reaction mixture was stirred at the temperature as described in Table S1 for several hours. A small sample was quenched in 50% aqueous (0.1%  $H_3PO_4$ ) MeCN and injected on HPLC immediately for analysis.

- b. **3** under the reaction conditions was partially cyclized to **10**,<sup>1</sup> which can be observed by HPLC. Note both **3b** and **10** converted to the *cis* amino alcohol **2** under borane reduction conditions. Therefore, *cis/trans* = (**3+10**) : 7.

### 3. Table S2. Substituent's effects on cyclopropanation



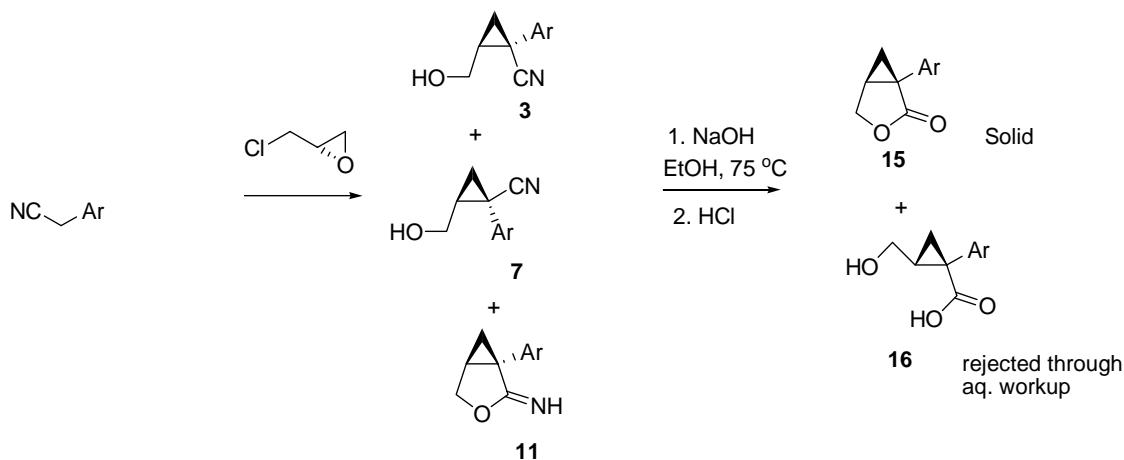
Ar	Solvents	NaHMDS	ee (%)	<i>cis/trans</i>
4-MeOC <sub>6</sub> H <sub>4</sub> -	THF	2.0 equiv	72.6	3.3:1
2-MeOC <sub>6</sub> H <sub>4</sub> -	THF	1.3 equiv	70.6	3.3:1
4-MeC <sub>6</sub> H <sub>4</sub> -	THF	2.0 equiv	75	3.6:1
4-MeC <sub>6</sub> H <sub>4</sub> -	(MeOCH <sub>2</sub> ) <sub>2</sub> /THF	2.0 equiv	76	5.7:1
4-MeC <sub>6</sub> H <sub>4</sub> -	PhMe	2.0 equiv	87.5	1.5:1
4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -	THF	1.3 equiv	96	6.5:1
3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -	THF	1.3 equiv	95	6.1:1
3-ClC <sub>6</sub> H <sub>4</sub> -	THF	1.3 equiv	92.6	6:1
3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> -	THF	1.3 equiv	96	5.7:1
4-ClC <sub>6</sub> H <sub>4</sub> -	THF	1.3 equiv	92	5.4:1
2-ClC <sub>6</sub> H <sub>4</sub> -	THF	1.3 equiv	94.3	3.5:1
2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> -	THF	1.3 equiv	91.2	1.1:1
4-BrC <sub>6</sub> H <sub>4</sub> -	THF	1.3 equiv	91.6	4.7:1
C <sub>6</sub> H <sub>5</sub> -	THF	1.3 equiv	86	4.1:1
4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -	THF	2.0 equiv	72	2.2:1

- a) All the reactions were carried out under the same conditions (NaHMDS, THF, -15 °C) except differences of the base charge and solvent as indicated in Table S2. S-(+)-epichlorohydrin is 98 ee%. NaHMDS (2.0M, THF) was used as base. For detailed, general experimental conditions, see Supporting Information, experimental section for the preparation of **4b**.
- b) *cis/trans* = (**3b+10b**) : **7b**
- c) ee was determined on the corresponding lactones by using chiral SFC or HPLC conditions. For details about determination of ee% of the cyclopropanation products, see Supporting Information, section 4.

#### 4. Determination of ee% of the cyclopropanation products

In order to determine the ee of the cyclopropanation products, the crude reaction mixture was directly subjected to hydrolysis (NaOH, aq. EtOH, 75 °C) to give the corresponding *cis* and *trans* acids.<sup>1,2</sup> The *cis* acid was easily lactonized to give **15** within 30 min at ambient temperature upon adjusting pH = 1 during the workup. The *trans* acid **16** was easily rejected through alkaline aqueous workup. Lactone **15** was used for ee% measurement.

**Scheme S1.** Preparation of lactone **15** through hydrolysis



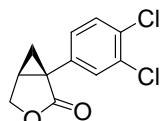
**Table S3.** Chiral SFC separation conditions<sup>\*</sup>

Substrates (racemic)	Ar	Retention time (min).
<b>15a</b> <sup>2c</sup>	4-MeC <sub>6</sub> H <sub>4</sub> -	6.0; 6.9
<b>15c</b>	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -	12.7; 15.4
<b>15d</b> <sup>2f</sup>	4-MeOC <sub>6</sub> H <sub>4</sub> -	8.0; 9.3
<b>15e</b> <sup>2a,b</sup>	C <sub>6</sub> H <sub>5</sub> -	5.6; 6.2
<b>15f</b> <sup>2d,e</sup>	4-ClC <sub>6</sub> H <sub>4</sub> -	6.0; 6.8
<b>15g</b>	4-BrC <sub>6</sub> H <sub>4</sub> -	7.5; 8.5
<b>15h</b>	3-ClC <sub>6</sub> H <sub>4</sub> -	5.8; 6.6
<b>15i</b>	3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -	3.0; 3.2
<b>15j</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -	3.8; 4.1
<b>15k</b> <sup>2g</sup>	2-ClC <sub>6</sub> H <sub>4</sub> -	6.3; 9.2
<b>15l</b>	2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> -	5.9; 8.2
<b>15m</b> <sup>2c</sup>	2-MeOC <sub>6</sub> H <sub>4</sub> -	7.8; 9.0

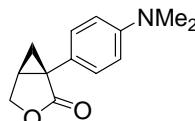
\* Column: Chiracel OF, 250x5 mm; flow rate: 1.5ml/min; modifier: isocratic 15% MeOH; pressure: 200bar; column temperature: 35 °C.

Normal phase chiral HPLC assay for **15b** (Ar = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-): Chiracel AD, 250x5 mm, isocratic *i*-PrOH/Hexane (5:95), 1.0ml/min.; Retention time: 16.9 and 18.7 min.

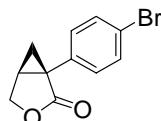
Characterization data of lactones **15**:<sup>1,2</sup>



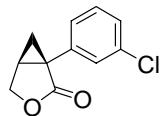
**(1R,5S)-1-(3,4-dichlorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (15b):**<sup>2c</sup> <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.53 (d, *J* = 2.1 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.30 (dd, *J* = 2.1, 8.4 Hz, 1 H), 4.48 (dd, *J* = 4.6, 9.4 Hz, 1 H), 4.32 (d, *J* = 9.3 Hz, 1 H), 2.60 (m, 1 H), 1.62 (dd, *J* = 4.9, 7.8 Hz, 1 H), 1.43 (t, *J* = 4.9 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 175.2, 134.6, 132.9, 132.1, 130.8, 130.4, 127.8, 68.2, 31.0, 25.5, 20.9.



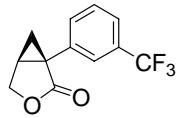
**(1R,5S)-1-[4-(dimethylamino)phenyl]-3-oxabicyclo[3.1.0]hexan-2-one (15c):** <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.28 (m, 2 H), 6.73 (m, 2 H), 4.46 (dd, *J* = 4.8, 9.2 Hz, 1 H), 4.27 (d, *J* = 9.2 Hz, 1 H), 2.95 (s, 6 H), 2.45 (m, 1 H), 1.60 (dd, *J* = 4.7, 7.9 Hz, 1 H), 1.29 (t, *J* = 4.7 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 176.8, 149.9, 129.4, 112.6, 68.1, 40.5, 31.3, 24.7, 19.5.



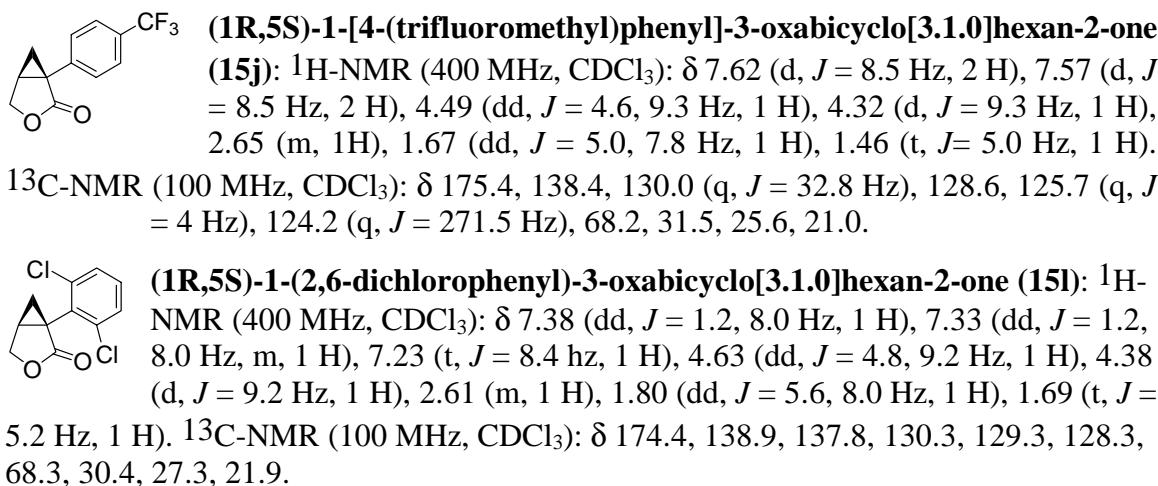
**(1R,5S)-1-(4-bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (15g):** <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.47 (d, *J* = 8.5 Hz, 2 H), 7.30 (d, *J* = 8.5 Hz, 2 H), 4.46 (dd, *J* = 4.7, 9.3 Hz, 1 H), 4.29 (d, *J* = 9.3 Hz, 1 H), 2.57 (m, 1 H), 1.61 (dd, *J* = 4.9, 7.8 Hz, 1 H), 1.39 (t, *J* = 4.9 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 175.7, 133.4, 131.9, 130.1, 121.9, 68.2, 31.4, 25.3, 20.6.



**(1R,5S)-1-(3-chlorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (15h):** <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.42 (m, 1 H), 7.28 (m, 2 H), 4.46 (dd, *J* = 4.4, 9.3 Hz, 1 H), 4.29 (d, *J* = 9.3 Hz, 1 H), 2.59 (m, 1 H), 1.63 (dd, *J* = 4.9, 7.8 Hz, 1 H), 1.39 (t, *J* = 4.9 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 175.2, 136.1, 134.4, 129.8, 128.3, 127.8, 126.4, 67.9, 31.2, 25.1, 20.4.



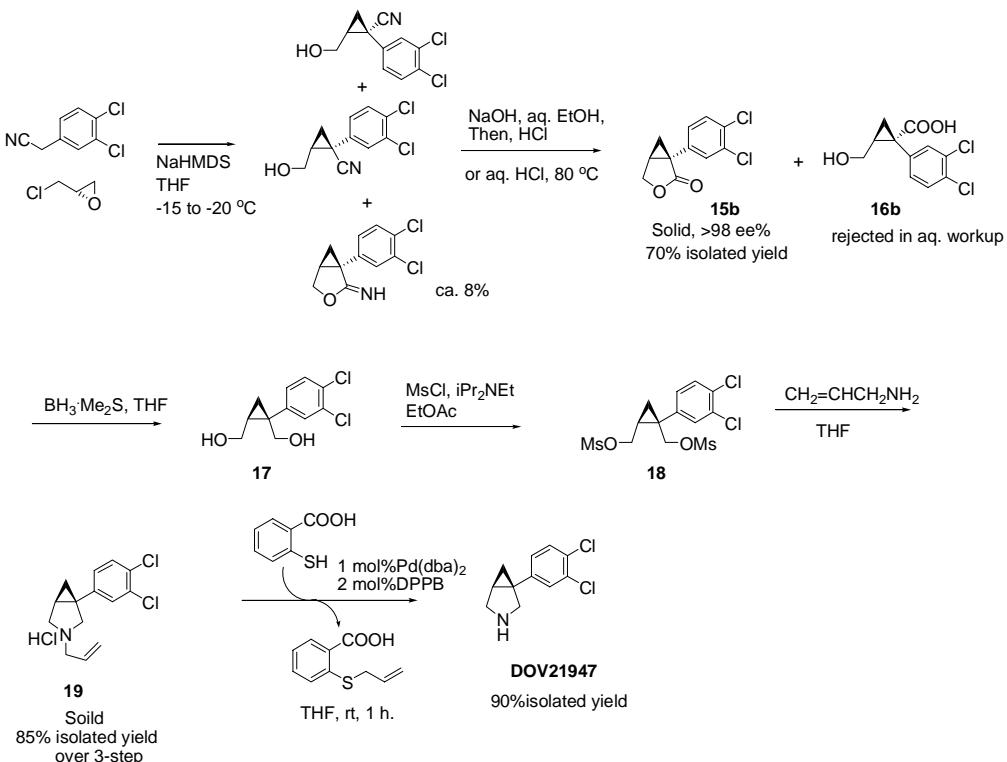
**(1R,5S)-1-[3-(trifluoromethyl)phenyl]-3-oxabicyclo[3.1.0]hexan-2-one (15i):** <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.67 (m, 2 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 4.50 (dd, *J* = 4.7, 9.3 Hz, 1 H), 4.33 (d, *J* = 9.3 Hz, 1 H), 2.65 (m, 1 H), 1.67 (dd, *J* = 4.9, 7.9 Hz, 1 H), 1.45 (t, *J* = 4.9 Hz, 1 H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 175.5, 135.5, 132.1, 131.2 (q, *J* = 32.8 Hz), 129.4, 125.1 (q, *J* = 4.0 Hz), 124.8 (q, *J* = 4.0 Hz), 124.0 (q, *J* = 272.3 Hz), 68.24, 31.63, 25.38, 20.75.



## 5. Alternative synthesis via lactone intermediate

A synthetic route through lactone **15b**, depicted in Scheme S2, was also identified. One of the advantages for this route is that the isolation of lactone **15b** is very straight forward since the *trans* acid **16b** can be easily rejected through an alkaline aqueous extraction. This route is efficient and only requires isolating two intermediates **15b** and **19**. Both **15b** and **19** can be prepared in one-pot. The overall yield for this 6-step synthesis is 53%.

**Scheme S2.** Lactone route to DOV21947

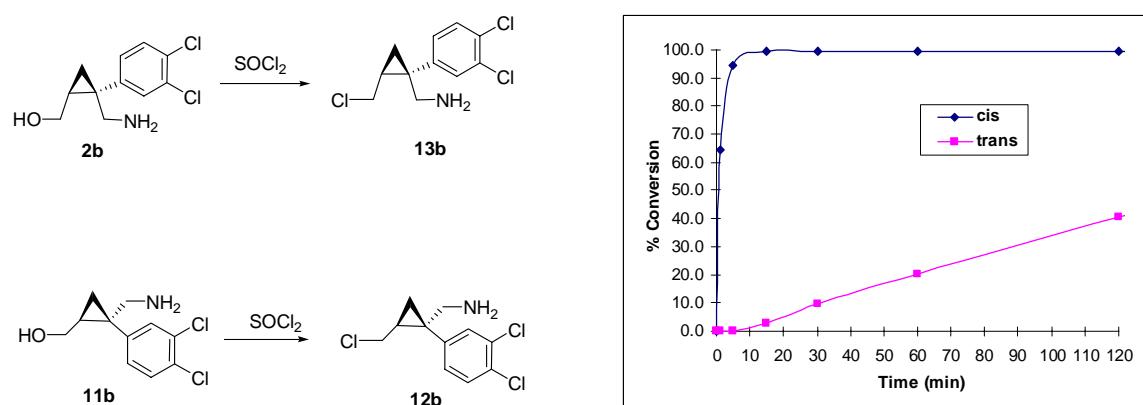


## 6. Unexpected reactivity of the *trans* chloride **12**

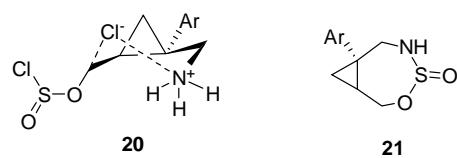
One of the keys to develop single through process to prepare 1-aryl-3-azabicyclo[3.1.0]hexanes is the unexpected lack of reactivity of the *trans* chloride **12**. To our surprise, the *trans* chlorides **12** do not behave as a competent alkylating agent in the presence of any nucleophilic species in the chlorination and cyclization sequence. In fact, the free-base **12b** was heated at 60 °C for 2 days in the presences of **1b** without observation of any dimerization or polymerization, or coupling product of **12b** and **1b**. Thus, the preparation of 1-aryl-3-azabicyclo[3.1.0]hexanes by avoiding isolation of any intermediates was achieved, since the *trans* chloride **12** formed during the cyclodehydration is not a concern as an electrophilic alkylating reagent to react with the final product **1**.

## 7. Kinetic observations of the chlorination of **2** and **11**

**Figure S1.** Kinetic profile of chlorination



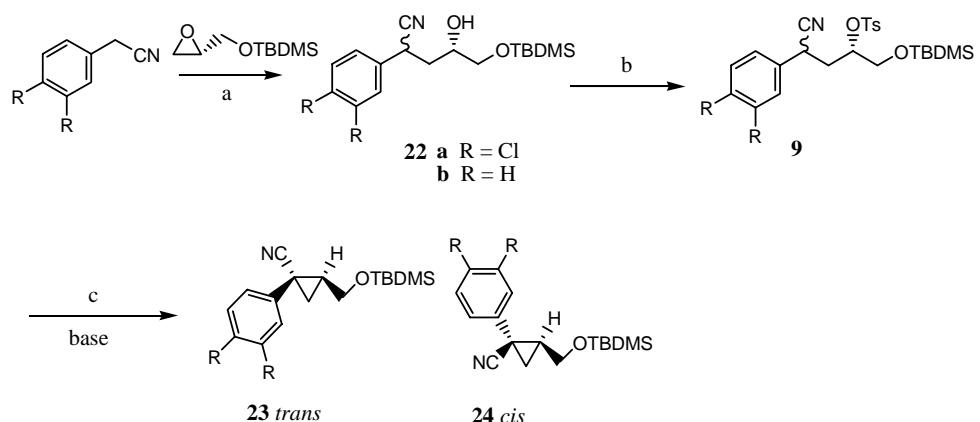
By carefully monitoring the chlorination of a mixture of amino alcohols **2** and **11**, we observed a significant reaction rate difference between **2** and **11**, as shown in Figure S1. The *cis* chloride **13**, presumably through the twist chair intermediate **20**, was formed significantly faster<sup>9</sup> than the *trans* chloride **12** in almost quantitative yield. The *cis* chloride **13** was cyclized to **1** immediately upon adjusting pH>8.5.<sup>3</sup> No possible intermediates such as **21** were observed.



## 8. Cyclopropanation through tosylate **9**

The tosylate intermediate for alternative cyclopropanation was prepared as depicted in Scheme S2. Treatment of arylacetonitrile and *tert*-butyldimethylsilyl *R*-(+)-glycidyl ether with *n*BuLi provided **22**. After aqueous workup, the crude product was directly used for the next step to prepare the sulfonyl derivatives **9** in the presence of DABCO in EtOAc. Intramolecular ring closure in the presence of base gave the cyclopropane products. For the summary of the solvent and base effects on the *cis/trans* ratio of the cyclopropane products, see Table 2.

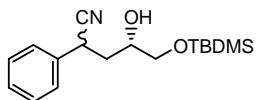
**Scheme S2.** Preparation of the cyclopropane **23/24**



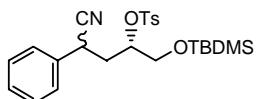
Reagents and conditions: (a) 1.0 equiv *n*-BuLi, 1.0 equiv. -78 to -25 °C, 30 min.; (b) 1.5 equiv TsCl, 2.0 equiv DABCO, EtOAc, rt, 30 min.; (c) cf Table 2 for combination of solvents and bases.

**Typical experimental procedures for the preparation of **9**:** To a solution of arylacetonitrile (50 mmol) and *tert*-butyldimethylsilyl *R*-(+)-glycidyl ether (9.42 g, 50 mmol) in THF (100 mL) at -78 °C was added *n*-BuLi (1.6 M in hexane, 31.3 mL, 50 mmol) dropwise.  $\text{BF}_3\text{-THF}$  (5.52 mL, 50 mmol) was slowly added. After addition, the reaction mixture was agitated for additional 15 min. at -78 °C, and then warmed to -25 °C. The reaction mixture was quenched into ice-cold, half-saturated  $\text{NH}_4\text{Cl}$  (200 mL). *t*-BuOMe (100 mL) was added and the separated organic phase was washed with 5%  $\text{NaHCO}_3$  (100 mL), brine (100 mL), and dried over  $\text{Na}_2\text{SO}_4$ . Upon concentration in vacuum, the crude diastereomeric mixture **22** was directly used for next step. For characterization, the 1:1 mixture of diastereomers was purified on silica gel column eluting with 20% EtOAc /hexane.

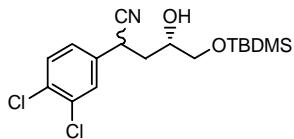
To a solution of the above diastereomeric mixture **22** and DABCO (11.2 g, 0.1 mol) in ethyl acetate (100 mL) was added tosyl chloride (14.3 g, 75 mmol) at ambient temperature. After aging 1 h at ambient temperature, the reaction mixture was diluted with ethyl acetate (375 mL) and water (375 mL). The separated organic layer was washed once with brine (375 mL) and dried over  $\text{Na}_2\text{SO}_4$ . Upon concentration in vacuum the crude diastereomeric tosylate **9** was purified on silica gel column eluting with 20% ethyl acetate/hexane.



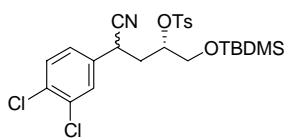
**(3S)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-hydroxy-2-phenylbutanenitrile 22b** (ca. 3:1 diastereomeric mixture):  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38 (m, 10 H, major + minor isomers), 4.22 (dd,  $J$  = 4.6, 11.3 Hz, 1H, major isomer), 4.10 (dd,  $J$  = 5.1, 10.2 Hz, 1H, minor isomer), 4.02 (1H, major isomer), 3.68 (dd,  $J$  = 3.5, 10.0 Hz, 1H, major isomer), 3.58 (dd,  $J$  = 3.5, 13.0 Hz, 1H, minor isomer), 3.45 (m, 2 H, major + minor isomers), 2.60 (s, br, OH, major isomer), 2.45 (s, br, OH, minor isomer), 2.19 (m, 1 H, minor isomer), 1.91 (m, 3 H, major + minor isomers), 0.92 (s, 9 H, major isomer), 0.90 (s, 9 H, minor isomer), 0.092 (s, 3 H, major isomer), 0.085 (3, 3 H, major isomer), 0.064 (s, 3 H, minor isomer), 0.055 (s, 3 H, minor isomer).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.53, 135.4, 129.4, 129.3, 128.4, 128.3, 128.11, 128.05, 127.4, 121.8, 120.8, 69.5, 68.0, 67.0, 66.7, 39.8, 38.9, 34.3, 33.3, 26.1, 18.5, -5.18, -5.24.



**(1S)-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-cyano-2-phenylethyl 4-methylbenzenesulfonate 9b** (1:1 diastereomeric mixture):  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.87 (d,  $J$  = 8.2 Hz, 2 H), 7.79 (d,  $J$  = 8.2 Hz, 2 H), 7.37 (m, 10 H), 7.27 (m, 4 H), 4.66 (m, 1 H), 4.45 (m, 1 H), 3.89 (t,  $J$  = 7.6 Hz, 1H), 3.79 (dd,  $J$  = 4.5, 11.2 Hz, 1 H), 3.68 (m, 4 H), 2.47 (s, 6 H), 2.30 (m, 3 H), 2.14 (m, 1 H), 0.85 (s, 9 H), 0.83 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H), -0.02 (s, 3 H), -0.05 (s, 3 H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  145.5, 145.4, 135.4, 134.9, 134.0, 133.6, 130.3, 130.2, 129.50, 129.48, 128.7, 128.6, 128.2, 128.1, 128.0, 127.3, 120.7, 120.0, 79.8, 78.8, 64.3, 63.8, 38.4, 37.5, 34.0, 33.0, 26.0, 25.9, 21.9, 18.4, 18.3, -5.3, -5.4.



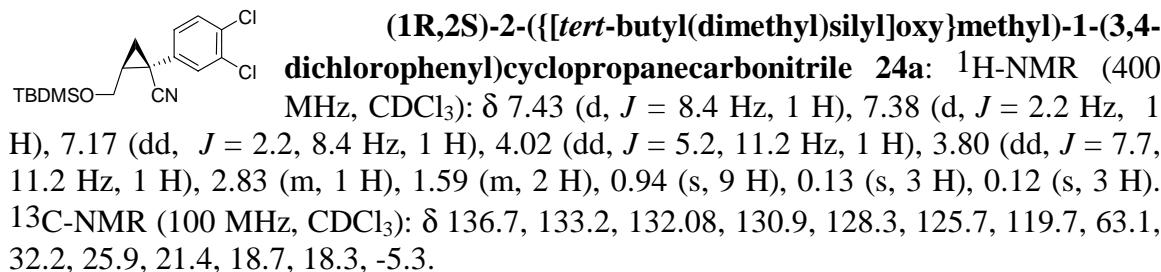
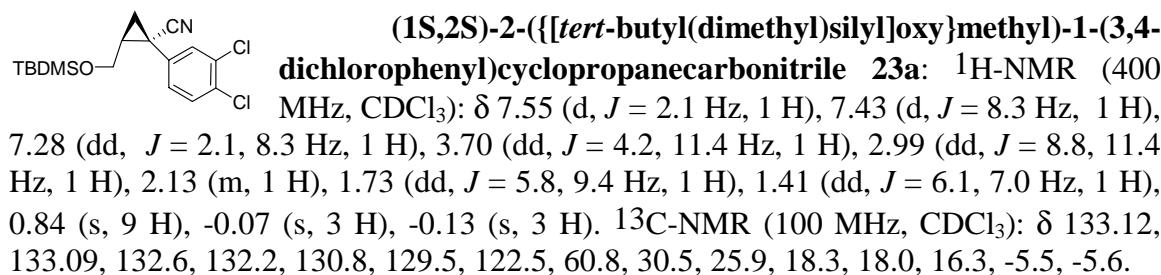
**(3S)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)-3-hydroxybutanenitrile 22a** (1:1 diastereomeric mixture):  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.48 (m, 4 H), 7.25 (m, 2 H), 4.19 (dd,  $J$  = 4.4, 11.3 Hz, 1 H), 4.09 (dd,  $J$  = 4.8, 10.4 Hz, 1 H), 3.99 (m, 1 H), 3.69 (dd,  $J$  = 3.6, 10.0 Hz, 1 H), 3.59 (dd,  $J$  = 3.3, 9.7 Hz, 1 H), 3.42 (m, 3 H), 2.58 (d,  $J$  = 3.9 Hz, 1 H), 2.42 (d,  $J$  = 4.3 Hz, 1 H), 2.16 (m, 1 H), 1.87 (m, 3 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.093 (s, 3 H), 0.087 (s, 3 H), 0.065 (s, 3 H), 0.060 (s, 3 H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.5, 135.5, 133.6, 133.5, 133.0, 132.7, 131.4, 131.3, 130.1, 129.5, 127.5, 126.8, 120.8, 119.9, 77.4, 69.3, 67.7, 66.9, 66.7, 39.6, 38.6, 33.6, 32.5, 26.1, 18.5, -5.2, -5.3.



**(1S)-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-cyano-2-(3,4-dichlorophenyl)ethyl 4-methylbenzenesulfonate 9a** (1:1 diastereomeric mixture):  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.86 (d,  $J$  = 8.3 Hz, 2 H), 7.79 (d,  $J$  = 8.2 Hz, 2 H), 7.46 (m, 2 H), 7.39 (m, 6H), 7.17 (m, 2 H), 4.64 (m, 1 H), 4.40 (m, 1 H), 3.92 (dd,  $J$  = 6.3, 8.7 Hz, 1 H), 3.84 (dd,  $J$  = 4.5, 11.2 Hz, 1 H), 3.69 (m, 2 H), 3.64 (m, 2 H), 2.48 (s, 6 H), 2.32 (m, 3 H), 2.10 (m, 1 H), 0.85 (s, 9 H), 0.82 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H), -0.02 (s, 3 H), -0.04 (s, 3 H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  145.7, 145.6, 135.4, 135.0, 133.8, 133.7,

133.4, 133.1, 131.5, 130.5, 130.4, 130.3, 130.0, 129.5, 128.2, 128.1, 127.4, 126.7, 119.9, 119.1, 79.3, 78.1, 64.2, 63.7, 38.3, 37.3, 33.3, 32.2, 26.0, 25.9, 22.0, 21.9, 18.4, 18.3, -5.3, -5.4.

**General procedure of cyclopropanation from tosylate **9**:** To a solution of tosylates **9** (1.0 mmol) in solvent as specified in Table 2 (4 mL) was added a solution of the base (1.05 mmol) as specified in Table 2 dropwise. After 1 h, HPLC assay indicated the starting tosylate was consumed. The reaction mixture was quenched with water (20 mL) and ethyl acetate (15 mL). The separated organic layer was washed with water (20 mL) and brine (20 mL), and then dried over  $\text{Na}_2\text{SO}_4$ . Upon concentration in vacuum, the product was purified on silica gel column eluting with 5% ethyl acetate/hexane to isolate the cyclopropanation products **23/24**, which also were further converted to **7/3** for characterization by treating with aqueous THF-TBAF.



## References

1. (a) Mouzin, G.; Cousse, H.; Bonnaud, B. *Synthesis* **1978**, 305. (b) Casadio, S.; Bonnaud, B.; Mouzin, G.; Cousse, H. *Boll. Chim. Fram.* **1978**, 117, 331. (c) Guilet, R.; Swartzentruber, J.; Loupy, A.; Petit, A.; Abeham, D.; Cousse, H.; Beaucourt, J. *C.R. Acad. Sci. Paris, I, Serie, II*, **1998**, 651.
2. For these literature-known compounds, the spectroscopic data were in full agreement with the reported data. (a) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamsihita, K.; Matsuda, A. *J. Org. Chem.* **1996**, 61, 915. (b) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, 2, 1145. (c) Kazuta, Y.; Tsujita, R.; Yamashita, K.; Uchino, S.; Kohsaka, S.; Matsuda, A.; Shuto, S. *Bioorg. Med. Chem.* **2002**, 10, 3829. (d) Shuto, S.; Shibuya, N.; Yamada, S.; Ohkura, T.; Kimura, R.; Matsuda, A. *Chem. Pharm. Bull.* **1999**,

---

47, 1188. (e) Kehler, J.; Hansen, T.; Poulsen, A.; Bjornholm, B.; Ruhland, T.; Norgaard, M. B.; Nielsen, S. M. *PCT Int. Appl.* **2005**, WO2005016884. (f) Rariy, R. V.; Heffernan, M.; Buchwald, S. L.; Swager, T. M. *PCT Int. Appl.* **2004**, WO2004039320. (g) Bonnaud, B.; Cousse, H.; Mouzin, G.; Briley, M.; Stenger, A.; Fauran, F.; Couzinier, J. P. *J. Med. Chem.* **1987**, *30*, 318.

3. The scope of this cyclorodehydration process will be reported in due course.