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Chiral Polycyclic Ketones via Desymmetrization of Dihaloolefins

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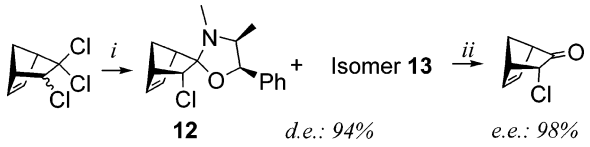
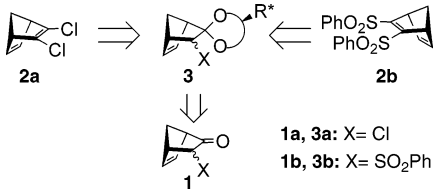


*(**i**): Elimination - desymmetrization;(**ii**) deprotection*

3-Chloronorbornenone (*R*)-**1a** (98% ee) was obtained from trichloronorbornene **5** in two steps by the in situ generation of dichloronorbornadiene **2a** with *t*-BuOK and desymmetrization with (−)-ephedrine, followed by hydrolysis with PPTS. The generality of this desymmetrization with (−)-ephedrine was tested with dibromonorbornadiene **2c** and other substituted dichloronorbornadienes.

Bicyclic ketones play a key role as building blocks in several total syntheses of natural products, thanks to their ability to simultaneously generate multiple stereocenters after the appropriate chemical transformations. For example, they are intermediates in the synthesis of prostaglandins,[1] of the antitumor echinosporin,[2] and of the dolabellane diterpenoids: claenone,[3a] stolonidiol,[3b] palominol,[3c] and dolabellatrienone.[3c] Furthermore, these structures represent the core of complex molecules, such as (−)-sordarin[4] and nonsteroidal estrogens.[5]

SCHEME 1. Retrosynthetic Approach



Customarily, the construction of the norbornenone unit is achieved by a Diels−Alder reaction between a cyclic diene and an electron-poor dienophile,[6] followed by basic hydrolysis.[7] In recent years, several different approaches have been developed in order to obtain enantiopure norbornenones by enantioselective cycloadditions catalyzed by chiral Lewis acids,[8] enzymatic resolution of 2-norborneol,[9] or chromatographic separation of the diastereoisomeric precursors.[10] Our research group has pursued the synthesis of enantiopure 3-phenylsulfonylnorbornenones through the desymmetrization of bis(phenylsulfonyl)norbonadienes by C_2 chiral diolates.[11]

We present in this paper an evolution of the original protocol, which uses the dichloroolefin **2a**, instead of the sulfonyl olefin **2b**, to produce the ketone **1a**[12] (a synthetic equivalent of **1b**) in the key desymmetrization step (Scheme 1). As **2a** was used as a precursor of **2b** in the first report,[13] the new synthetic route presents, according to the atom-economy rule,[14] the advantage of significantly reducing the molecular weights of the reagents (i.e., the number of atoms) and the number of steps. As the norbornenone core is usually required in the early stages of natural product syntheses, the requisites of rapidity and inexpensiveness in the production of this building block may be appreciated. The bicyclic structure **2a** is readily available via a Diels−Alder reaction of the inexpensive reagents trichloroethylene and cyclopentadiene,[15] followed by elimination with base.

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SCHEME 2. Synthesis of Acetals 6

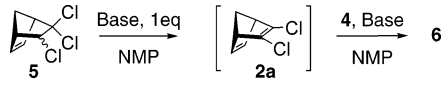
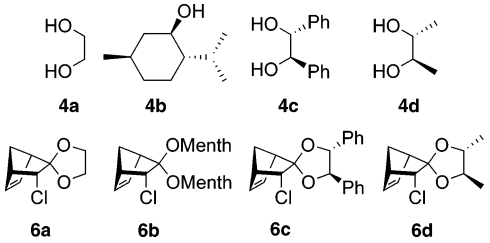


TABLE 1. Reaction Conditions of 5 with Alcoholates and Diols 4



	base	alcohol or diol **4**	**4**:**5** ratio	product **6**	time	temp (°C)	conv[a] (%)	de[a] (%)
1	*t*-BuONa	**4a**	3.5:1	**6a**	3 days	80	20	
2	*t*-BuOLi	**4a**	3.5:1	**6a**	3 days	80		
3	*t*-BuOK	**4a**	3.5:1	**6a**	24 h	80	70	
4	*t*-BuOK	**4b**	2:1	**6b**	48 h	80	<5	61
5	*t*-BuOK	**4c**	1:1	**6c**	48 h	80	<5	66
6	*t*-BuOK	**4d**	1:1	**6d**	12 h	60→80	70	2

[a] Calculated on the basis of NMR spectra.

Our studies come as an extension of the substitution reaction we applied to the synthesis of perfunctionalized benzocyclotrimers,[16] by replacing the thiol nucleophiles with the alcoholates and diols **4**. The synthetic protocol is represented in Scheme 2, and the results are summarized in Table 1.There are only a few examples of nucleophilic substitution by alcoholates on halogenated alkenes.[17]

The acetalic products **6** are obtained in one pot from **5**,[15] after elimination with 1 equiv of base. To assess the best reaction conditions, **5** was initially reacted with ethylene glycol **4a** using different *tert*-butanolate salts, as suggested in the literature.[18]

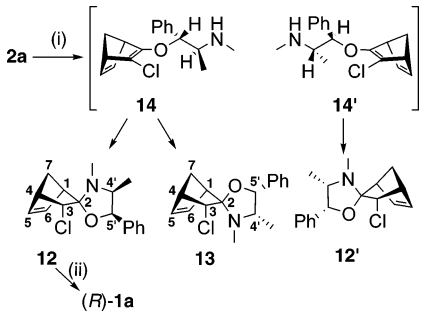
When the reaction was carried out with *t*-BuONa (Table 1, entry 1), the formation of **2a** was observed after 24 h at 80 °C and the acetal **6a** after 3 days in low conversion. When the base *t*-BuOLi was employed (entry 2), the selective elimination of the *exo*-proton of **5** was observed, while **6a** was not detected, even at higher temperature and with longer reaction times. These data suggest that the use of *t*-BuOK as base for 24 h (entry 3) is best for this reaction.

The role of steric hindrance in the chiral process was evaluated by reacting **5** with the alcohol **4b** and the diols **4c** and **4d** (entries 4−6). The larger auxiliaries **4b** and **4c** induce enantioselectivity, although at low conversion, while **4d** is more reactive but gives two diastereoisomers in a 1:1 ratio. The neutral workup procedure[12] used for all these experiments led to the isolation of a single epimer with the *exo* orientation of the H_3 proton (from the detection of NOESY dipolar interactions with the methano bridge).

These results led to the following considerations. According to the Ad_N-E mechanism generally assumed for this reaction,[11] the diastereoselectivity of **4c** (entry 5) may be due to the initial approach of the alcoholate to the vinyl bond, in which the bulky group plays a key role; on the other hand, its steric hindrance might prevent the second ring closure. Opposite considerations may be done for entry 6: the methyl groups of **4d** are not bulky enough to induce diastereoselectivity on the first addition step but are sufficiently small to allow the ring-forming acetalization.

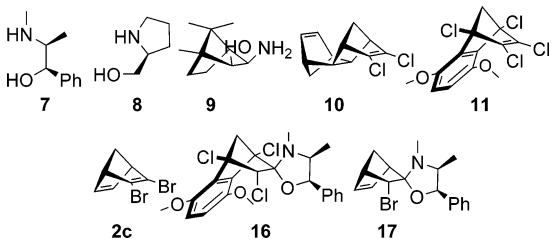
The aforementioned remarks led us to take into account the use of nonsymmetric chiral auxiliaries in order to induce the required high stereoselectivity during the first addition step, while at the same time allowing the successive ring-closing acetalization. The easily available aminoalcohols **7**−**9**[19] provide a series of appropriate, inexpensive chiral auxiliaries. The reaction, exemplified in Scheme 3 for **2a**, is general for substrates **10**, **11**, and **2c**, as shown in Table 2. In principle, the addition of (−)-ephedrine[20] may occur at the *pro-R* or *pro-S* faces of the dichlorovinyl double bond and from the *endo* or *exo* directions. Actually, the ^{1}H NMR spectrum of the reaction crude shows only three doublets at about δ 5.1 and in the intensity ratios 85:12:3, attributed to $H_{5'}$ of the oxazolidine ring, that exactly match, in terms of intensity, three doublets at about δ 4.4, attributed to H_3 of the norbornene unit.

SCHEME 3. Synthesis[a] of Oxazolidines 12, 12′, 13, and Ketone (*R*)-1a[12]



[a] Reagents and conditions: (i) 1.5 equiv of **7**, *t*-BuOK, NMP, 16 h, 80 °C; (ii) PPTS (pyridinium *p*-toluenesulfonate), H_2O−THF, 2 days, rt.

TABLE 2. Yields and Diastereoselectivity of the Reaction of Dihaloalkenes with Aminoalcohols



	substrate	aminoalcohol	product	yield (%)	de (%)
1	**2a**	**7**	**12**	90	94[a]
2	**2a**	**8**	**1a**	80	33[b]
3	**2a**	**9**	**1a**	82	60[b]
4	**10**	**7**			
5	**11**	**7**	**16**	70	93[a]
6	**2c**	**7**	**17**	90	94[a]

[a] Calculated on the basis of ^{1}H NMR spectra. [b] Taken as the ee of (*S*)-**1a** over (*R*)-**1a** (from chiral GC analysis).

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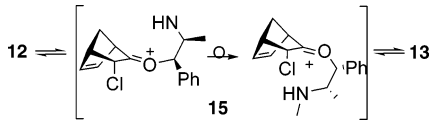
SCHEME 4. Isomerization of 12 into 13



The NOESY analysis of a sample (obtained as described below), where the major and the intermediate isomers are in an approximate 1:1 ratio, is consistent with the determined structure of **12** (see below) and also allows the assignment of the configuration of **13** (with inverted orientation of the oxazolidine ring) to the intermediate substance. The mother liquor, collected from the crystallization process, is sufficiently enriched in the minor isomer for a NOESY analysis, allowing the assignment of the configuration of **12′**. The details of the NOESY analyses are reported in the Supporting Information. Thus, the diastereoisomeric excess (de) for the desymmetrization process is 94% on the *pro-R* face.

The major product can be easily separated by crystallization from pentane and is characterized as **12** by an X-ray crystal structure analysis (see Supporting Information).

As for the mechanism, these findings agree with an Ad_N-E approach of the oxygen base of (−)-ephedrine **7** exclusively to the dichlorovinyl *exo* face of **2a**, with a strong preference for the *pro-R* approach over the *pro-S* one, and formation of the diastereoisomeric vinyl ethers **14** and **14′**.

There follows the Ad_N closure of nitrogen, which is easier from the *exo* direction (although Ph and Me are pushed toward the chlorine atom) than from the *endo* orientation: thus the major **14** vinyl ether gives the **12** and the **13** isomers in an 88:12 ratio, while from the minor ether **14′** we can detect only the formation of **12′**.

The position of the Ph group in **14**, which is oriented away from the chlorine atom, explains the preference for the isomers **12** and **13** in the desymmetrization process.

After the ring closure, chlorine is pushed by protonation into the *endo* direction and the steric interaction in **12** between chlorine and Ph becomes more important. As a matter of fact, in an acidic contest (the case was monitored by NMR in $CDCl_3$ for 14 days), the new equilibrium of 59:41 between **12** and **13** is reached. The oxacationic intermediate **15** is proposed (Scheme 4), where the chlorine atom maintains the *endo* orientation, and neither epimerization nor deuteration (these occurrences are not actually observed) are permitted.

The desymmetrization process of **2a** was also tested with the aminoalcohols L-prolinol **8** and (2*S*)-3-*exo*-aminoisoborneol **9**[21] (entries 2 and 3 in Table 2). The degree of conversion can be established from observation of the vinylic region of the ^{1}H NMR spectra, while the single adducts (ethers or oxazolidine) could neither be separated nor characterized. The de for the desymmetrization process is then taken as the ee measured by chiral GC analysis (see Supporting Information) for the (*S*)-**1a** and (*R*)-**1a** chloroketones, obtained from the crude mixture by the action of PPTS in THF−H_2O (Table 2).

These results highlight the efficiency of (−)-ephedrine **7** as a chiral auxiliary. It was then tested with haloolefins **10**,[15] **11**,[22] and **2c**[23] (entries 4−6). Olefin **10** was unreactive, probably because of stronger steric hindrance. On the other hand, (−)-ephedrine proved to be adequately efficient with substrates **11** and **2c**. The major diastereoisomers **16** (subjected to an X-ray crystal structure analysis; see Supporting Information) and **17** were purified by crystallization.

The synthesis, presented in this paper, of bicyclic ketones with excellent ee offers several advantages: among them, the use of inexpensive reagents, the short synthetic sequence, the high crystallinity of the products, and the mild conditions, described in the literature,[24] required for the removal of the auxiliary and the halogen atom.

The potential extension of this protocol has been tested with haloolefins **11** and **2c**, which are representative of a wide variety of substrates containing the dihalovinyl moiety.[25] The protocol can be exploited for other chemical transformations of dichloroolefins, recently reported.[26]

Experimental Section

General Procedure for the Reaction of Dihaloolefins with Amino Alcoholates, Alcohols, and Diols: 1.5 equiv of aminoalcoholates, or alcoholates or diolates **4**, prepared in situ by reaction with base (3 equiv), in dry NMP (10 mL), was added to a solution of 1.0 equiv of dihaloolefins **10**, **11**, or **2c** in dry NMP (5 mL). **2a** was previously prepared in situ by reacting **5** with 1.0 equiv of base. After 16 h at 80 °C under an Ar atmosphere, the cooled reaction mixture was treated with H_2O (20 mL) and extracted with *n*-pentane (3 × 20 mL); the combined organic layers were dried over $MgSO_4$, and the solvent was eliminated. Products **6** were purified no further. Products **12**, **16**, and **17** were isolated by crystallization from *n*-pentane. Products **13** and **12′** could not be purified further and were analyzed in a mixture by ^{1}H NMR, COSY, and NOESY experiments. **6a:** oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.13 (2H, AB system), 4.14 (1H, d, J = 3.7 Hz), 4.02−3.97 (3H, m), 3.94−3.89 (1H, m), 3.06 (1H, m), 2.76 (1H, m), 1.83 (1H, dm, J = 9.6 Hz), 1.81 (1H, dm, J = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.1, 134.9, 114.6, 66.9, 65.7, 64.6, 50.5, 47.6, 45.2. **6d:** oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30 (2H, AB system), 4.10 (1H, d, J = 3.4 Hz), 3.73−3.53 (2H, m), 3.06 (1H, m), 2.72 (1H, m), 3.00 (1H, m), 1.84 (1H, dm, J = 9.5 Hz), 1.74 (1H, dt, J = 9.5, 1.9 Hz), 1.24 (6H, m). **6d′:** oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.31 (2H, AB system), 4.18 (1H, d, J = 3.4 Hz), 3.67 (2H, m), 3.03 (1H, m), 2.79 (1H, m), 1.80 (2H, AB system), 1.26 (6H, m);

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IR (neat) ν_{max} (cm^{-1}) 3452, 2979, 2878, 1726, 1455, 1280, 1190, 1080, 727, 697, 581. **12:** solid; mp 116.2 °C; $[\alpha]_D = -43$ (c = 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42 (2H, d, J = 7.0 Hz), 7.27 (2H, t, J = 7.3 Hz), 7.21 (1H, t, J = 7.2 Hz), 6.38 (2H, AB system), 5.06 (1H, d, J = 7.9 Hz), 4.45 (1H, d, J = 3.4 Hz), 3.23 (1H, dq, J = 6.5, 1.3 Hz), 3.12 (1H, m), 3.09 (1H, m), 2.47 (3H, s), 1.79 (1H, dm, J = 9.8 Hz), 1.79 (1H, dt, J = 9.8, 1.9 Hz), 0.71 (3H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2, 137.8, 135.8, 127.8, 127.7, 127.4, 102.9, 80.8, 65.3, 61.6, 48.0, 44.9, 43.9, 34.7, 15.4; IR (KBr) ν_{max} (cm^{-1}) 3435, 2971, 2805, 1651, 1574, 1494, 1457, 1334, 1100, 766, 755, 585, 470. Anal. Calcd for $C_{17}H_{20}ClNO$: C, 70.46; H, 6.96; N, 4.83. Found: C, 70.37; H, 6.78; N 4.49. **13:** ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (2H, d, J = 4.4 Hz), 7.28−7.19 (3H, m), 6.38 (2H, AB system), 5.02 (1H, d, J = 7.6 Hz), 4.38 (1H, d, J = 3.8 Hz), 3.86 (1H, q, J = 7.0 Hz), 3.14 (1H, m), 3.07 (1H, m), 2.44 (3H, s), 2.16 (1H, dm, J = 8.8 Hz), 1.85 (1H, dt, J = 9.0, 1.9 Hz), 0.82 (3H, d, J = 6.9 Hz). **12′:** ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29 (2H, d, J = 5.2 Hz), 7.27−7.19 (3H, m), 6.5 and 6.36 (2H, AB system), 5.13 (1H, d, J = 7.5 Hz), 4.35 (1H, d, J = 3.6 Hz), 3.40 (1H, q, J = 7.1 Hz), 3.09 (1H, m), 3.07 (1H, m), 2.42 (3H, s), 1.85−1.74 (2H, m), 0.73 (3H, d, J = 6.6 Hz). **16:** solid; mp 155.2 °C; $[\alpha]_D = +51$ (c = 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26 (2H, d, J = 8.3 Hz), 7.25−7.19 (3H, m), 6.76 (1H, d, J = 9.0 Hz), 6.73 (1H, d, J = 9.0 Hz), 5.52 (1H, d, J = 8.1 Hz), 4.60 (1H, s), 4.08 (1H, dq, J = 6.4, 1.6 Hz), 3.82 (3H, s), 3.82 (3H, s), 2.88 (1H, d, J = 9.8 Hz), 2.87 (3H, s), 2.85 (1H, d, J = 9.8 Hz), 0.58 (3H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.7, 150.6, 138.9, 131.2, 128.7, 127.7, 127.4, 127.3, 113.8, 113.4, 100.6, 82.0, 74.7, 70.9, 68.6, 60.4, 59.8, 56.9, 56.6, 31.9, 15.7; IR (KBr) ν_{max} (cm^{-1}) 3421, 3008, 2974, 2831, 1606, 1475, 1460, 1256, 1206, 1027, 1016, 754, 701, 565, 477. Anal. Calcd for $C_{23}H_{24}Cl_3NO_3$: C, 58.93; H, 5.16; N, 2.99. Found: C, 58.71; H, 4.84; N, 3.12. **17:** solid; mp 136.6 °C; $[\alpha]_D = -55$ (c = 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (2H, d, J = 7.0 Hz), 7.26 (2H, t, J = 6.8 Hz), 7.22 (1H, t, J = 7.0 Hz), 6.37 (2H, AB system), 5.06 (1H, d, J = 8.1 Hz), 4.51 (1H, d, J = 3.3 Hz), 3.22 (1H, dq, J = 6.5, 1.5 Hz), 3.17 (1H, m), 3.08 (1H, m), 2.46 (3H, s), 1.85 (2H, m), 0.70 (3H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1, 137.9, 136.7, 128.1, 127.6, 127.4, 101.2, 80.9, 61.4, 57.0, 48.3, 45.1, 43.8, 34.6, 15.6; IR (KBr) ν_{max} (cm^{-1}) 3400, 3069, 2973, 2871, 1685, 1493, 1455, 1333, 1197, 757, 613, 583, 470. Anal. Calcd for $C_{17}H_{20}BrNO$: C, 61.09; H, 6.03; N, 4.19. Found: C, 61.20; H, 6.28; N, 4.49.

Synthesis of Ketone (*R*)-1a: A solution of **12** (220 mg, 0.76 mmol) and PPTS (190 mg, 0.76 mmol) in THF (5 mL) and H_2O (5 mL) was stirred at rt for 2 days and then diluted with 20 mL of water and extracted with pentane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$. The crude reaction product was purified by Kugelrohr giving (*R*)-**1a** (90 mg, 83%, ee = 98%, GC) as oil. Spectral data were identical to those reported in literature: IR (neat) ν_{max} (cm^{-1}) 1758 stretching C=O (lit.[12c] 1750); $[\alpha]_D = +518$ (c = 0.26, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.57 (1H, m), 6.22 (2H, m), 4.10 (1H, d, J = 3.5 Hz), 3.33 (1H, m), 3.22 (1H, m), 2.38 (1H, dm, J = 10.2 Hz), 2.07 (1H, dm, J = 10.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.8, 140.7, 131.3, 56.9, 54.6, 46.2, 45.8; MS (EI, 70 eV) m/z 142 (M^+, 40), 113 (6), 79 (100), 66 (75), 51 (45) 39 (55).

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Supporting Information Available: Crystallographic data, NMR data, and experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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