Pergamon

Tetrahedron Letters 40 (1999) 8007–8010

TETRAHEDRON LETTERS

Synthesis of chiral crownophanes via tandem Claisen rearrangement

Hideo Tokuhisa,[a] Yoshinobu Nagawa,[a] Hirotaka Uzawa[b] and Kazuhisa Hiratani[a,*]

[a]*National Institute for Advanced Interdisciplinary Research, 1-1-4 Higashi, Tsukuba, Ibaraki 305-8562, Japan*
[b]*National Institute of Materials and Chemical Research, 1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan*

Received 8 June 1999; revised 24 August 1999; accepted 27 August 1999

Abstract

A synthetic route for crownophanes containing a chiral binaphthyl unit using tandem Claisen rearrangement is described to demonstrate the versatility of this approach. Molecular recognition by the resulting crownophane for butylurea is also investigated.

Keywords: chiral crownophanes; Claisen rearrangement; molecular recognition; CD; binaphthyl.

Crownophanes, macrocycles containing rigid aromatic moieties and flexible oligoethylene glycol moieties, have been studied extensively because they are expected to show specific, hybridized properties and functions compared to basic macrocycles, such as crown ethers,[1] calixarenes,[2] etc. For example, a macrocyclic polyether containing a linked acidic group forms a complex even with a very weak base, such as urea.[3] Calixarene derivatives having both a chiral component and a chromophore enable us to detect the chirality by the naked eye.[4] The synthetic methods of crownophanes, however, tend to be laborious because of the complicated structure.

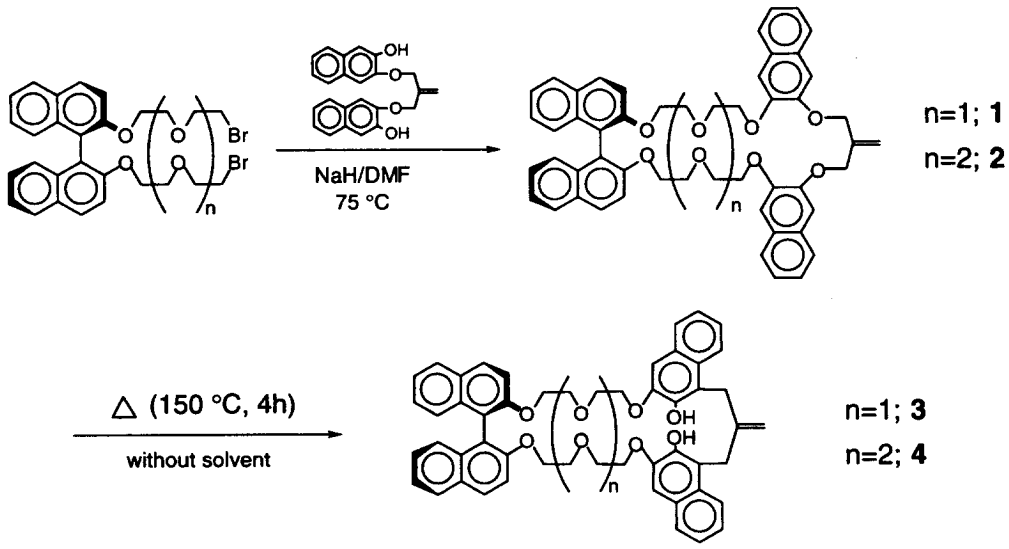
We have recently found that 1,1-bis(aryloxymethyl)ethylene derivatives can be converted thermally to bis(hydroxyaryl) derivatives in high yields by Claisen rearrangement, which we call a 'tandem Claisen rearrangement'.[5] The reaction provides a new, simple way to synthesize crownophanes having several phenolic moieties.

In this work, to demonstrate the versatility of this approach for preparing crownophanes, we have synthesized crownophanes **3** and **4** incorporating an axially asymmetric binaphthyl unit as a rigid moiety as well as a chiral component into the macrocycles via tandem Claisen rearrangement, as shown in Scheme 1.

Crownophanes **3** and **4** were prepared from enantiomerically pure (*R*)-(+)-1,1′-bi-2,2′-naphthol as the starting material. The binaphthol was first etherified with 2-(2-chloroethoxy)ethanol or 2-[2-(2-chloroethoxy)ethoxy]ethanol protected by 3,4-dihydro-2*H*-pyran, and then brominated directly with

* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01662-7



Scheme 1. Synthetic route of chiral crownophanes via tandem Claisen rearrangement

triphenylphosphonium bromide.[6] The mixed solution of the brominated compounds and a 2-methylene-1,3-bis(3-hydroxynaphthyl-2-oxy)propane was added dropwise to a DMF solution containing NaH as a base at 75°C for 20 h. After removing the solvent under vacuum, the residue was extracted with chloroform, washed with water, and dried over anhydrous $MgSO_4$. After evaporation of chloroform, the residue was subjected to column chromatography on silica gel with ethyl acetate:$CHCl_3$ (10:90) as an eluent. Macrocyclic polyethers, precursors **1** and **2** of target compounds **3** and **4**, respectively, were yielded as main products (**1**: yield 31%, R_f=0.63; **2**: yield 43%, R_f=0.09).

Tandem Claisen rearrangement of precursors **1** and **2** proceeded almost quantitatively without a solvent at 150°C for 4 h under vacuum. The reaction products were purified by a column chromatography on silica gel with ethyl acetate:$CHCl_3$ (10:90) (**3**: R_f=0.26, **4**: R_f=0.03).[7]

^{1}H NMR spectra of the smaller macrocyclic compounds **1** and **3**, and larger ones **2** and **4** offer some structural information concerning crownophanes (Fig. 1). The line shape of the peak at 4.85 ppm based on the sp^3 methylene protons of the isobutenyl group is an AB quartet on 300 MHz ^{1}H NMR spectrum for the smaller precursor **1**, while it is singlet for the larger one, **2**, indicating that the smaller macrocyclic polyether is more rigid, thereby affording a slow rotation rate of the methylene moieties on the NMR time scale. After tandem Claisen rearrangement, the proton peak arising from the generated hydroxyl group for the macrocycle **3** is observed more upfield (6.75 ppm), compared to the larger compound **4** (7.08 ppm). This might show the different degree of hydrogen bonding for the phenolic hydroxyl groups of the crownophanes.

Also taken were ^{1}H NMR spectra of the crownophanes during tandem Claisen rearrangement at different temperatures, showing rearrangement occurred even at 100°C. However, it is noteworthy that one time rearranged compounds, whose characteristic peaks appeared at 4.73, 4.79, and 5.21 ppm due to the isobutenyl group, were yielded as the main product at 100°C. At 120°C the reaction was almost complete after 15 h. There was no significant difference in the progress of the thermal reaction between the smaller and larger macrocycles.

Optical rotations of the crownophanes **1**, **2**, **3**, and **4** were also measured. Interestingly, there is a significant difference between the smaller macrocycle and larger one in the rotation changes after tandem Claisen rearrangement: the rotation increased from $[\alpha]^{29}_D$ +46° for **1** to $[\alpha]^{29}_D$ +57° for **3**, while it

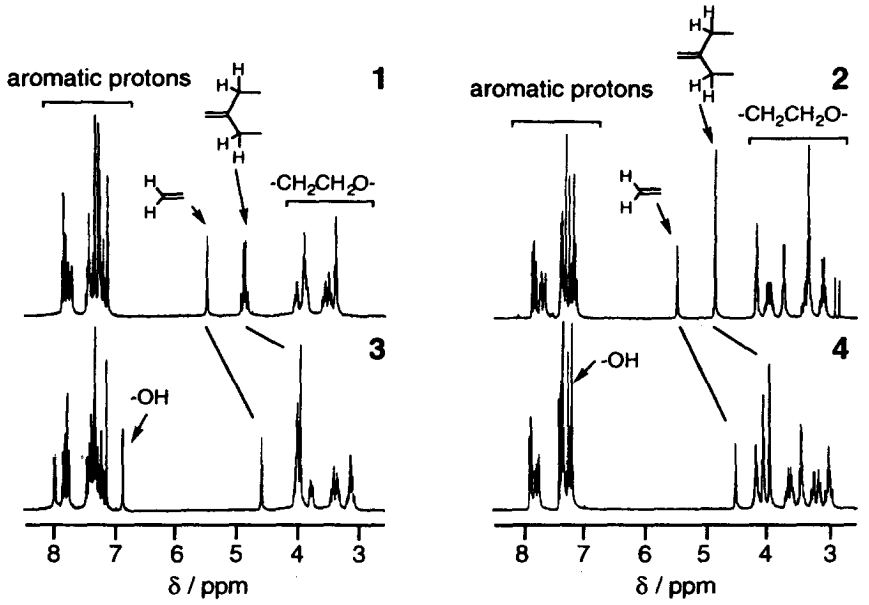


Figure 1. ^{1}H NMR spectra of crownophanes **1**, **2**, **3**, and **4** in $CDCl_3$

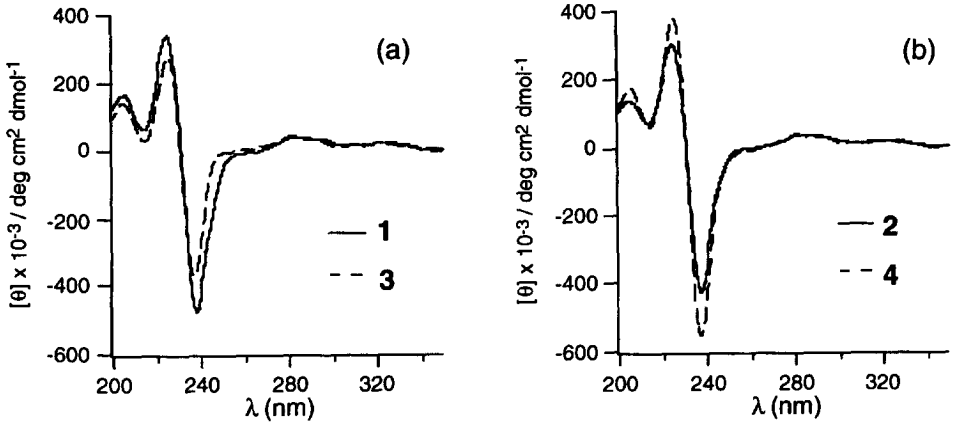


Figure 2. CD spectra of: (a) smaller macrocyclic compounds **1** and **3**; and (b) larger macrocyclic compounds **2** and **4** in acetonitrile

decreased from $[\alpha]^{29}_D$ +36° for **2** to $[\alpha]^{29}_D$ +9.3° for **4** (c=0.67, CH_2Cl_2). On the other hand, the enantiomer excesses determined by HPLC[8] were kept at high values (**3**: 91%, **4**: 93%) even after the thermal rearrangement. Additionally, the circular dichroism (CD) spectra of the crownophanes were measured (Fig. 2). As shown in the figures, all of the crownophanes have similar, strong negative and positive Cotton effects at ca. 236 and 224 nm, respectively. Thus the absolute configurations of the binaphthyl units were affected little by the thermal rearrangement. These facts taken together, indicate that the tandem Claisen rearrangement of the chiral crownophanes did not cause significant racemization.

As a preliminary study to assess crownophane **4** as a host molecule, we have investigated the complexation between **4** and butylurea with ^{1}H NMR. We chose butylurea for the following reasons: (1) it has two hydrogen-bonding acceptor and three donor sites, while the crownophanes have two donor and several acceptor sites; two phenolic hydroxyl groups and several ether oxygens; (2) it easily dissolves in

$CDCl_3$ and; (3) the methyl peak in a ^1H NMR spectrum appears at region barren of peaks arising from the crownophanes, making it easier to calculate the ratio of the crownophane to the urea in $CDCl_3$. Although there was no significant chemical-shift of the relevant peak in the ^1H NMR spectrum of the crownophane at 21°C after adding three times molar excess of butylurea, we observed some interesting phenomena indicating the complexation between **4** and butylurea at −50°C: (1) there was a significant downfield-shift and broadening of the peak due to hydroxyl-protons to 8.24 ppm; (2) the methyl proton peak of butylurea shifted upfield from 0.92 to 0.86 ppm, while the peak for a solution containing only butylurea remained unchanged at 0.93 ppm and; (3) integration of the relevant peaks showed approximately 1:1 complexation of butylurea to the crownophane in the mixed solution at −50°C. Therefore, we conclude that crownophane **4** might form a 1:1 complex with butylurea at −50°C.

In conclusion, tandem Claisen rearrangement afforded crownophanes containing a chiral binaphthyl moiety in good yields without significant racemization. The complexation of the resulting crownophane **4** with butylurea at −50°C was confirmed by ^1H NMR spectra. These crownophanes are also expected to show chiral recognition. At present we have obtained a result that the crownophane **3** has a higher affinity for the (*R*)-phenylglycinol rather than the (*S*)-isomer: K_a=12 for the (*R*)-isomer; K_a=6.9 for the (*S*)-isomer.[9]

References

1. Izatta, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1991**, *92*, 1721.
2. Gutsche, C. D. Calixarenes. *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989.
3. Aarts, V. M. L. J.; van Staveren, C. J.; Grootenhuis, P. D. J.; van Eerden, J.; Kruise, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035.
4. Kubo, Y.; Hirota, N.; Maeda, S.; Tokita, S. *Anal. Sci.* **1998**, *14*, 183.
5. Hiratani, K.; Takahashi, T.; Kasuga, K.; Sugihara, H.; Fujiwara, K.; Ohashi, K. *Tetrahedron Lett.* **1995**, *36*, 5567.
6. Stock, H. T.; Kellogg, R. M. *J. Org. Chem.* **1996**, *61*, 3093.
7. Compound **3**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.17–3.30 (4H, m), 3.34–3.39 (4H, m), 3.80–3.87 (2H, m), 3.93 (4H, s), 4.01–4.09 (6H, m), 4.55 (2H, s), 6.69 (2H, s), 7.06–7.12 (4H, m), 7.18–7.23 (2H, m), 7.27–7.40 (8H, m), 7.69–7.80 (6H, m), 7.89–7.92 (2H, m); FT-IR (KBr): 3448, 1624, 1270, 1116; FAB-MS (pos): m/z 798 (M^+). Anal. calcd (found) for $C_{52}H_{46}O_8$ +0.5H_2O: C, 77.30 (77.47); H, 5.86 (5.58). Compound **4**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05–3.18 (4H, m), 3.20–3.35 (4H, m), 3.45–3.48 (4H, m), 3.51–3.70 (4H, m), 3.95 (4H, s), 4.06–4.10 (4H, m), 4.12–4.24 (4H, m), 4.47 (2H, s), 7.04–7.07 (2H, d), 7.10 (2H, s), 7.16–7.21 (4H, m), 7.24–7.32 (6H, m), 7.33–7.36 (2H, d), 7.67–7.72 (4H, m), 7.80–7.83 (4H, m); FT-IR (KBr): 3448, 1620, 1270, 1123; FAB-MS (pos): m/z 886 (M^+). Anal. calcd (found) for $C_{56}H_{54}O_{10}$+H_2O: C, 74.32 (74.50); H, 6.24 (6.03).
8. For the determination of the ee, a chiralpak AD column with ethanol was used.
9. The association constants, K_a, were determined by a NMR titration method in $CDCl_3$ at room temperature.