Tetrahedron 67 (2011) 6073–6082

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient and diversity-oriented total synthesis of Riccardin C and application to develop novel macrolactam derivatives

Masazumi Iwashita, Shinya Fujii, Shigeru Ito, Tomoya Hirano, Hiroyuki Kagechika *

Graduate School of Biomedical Science, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

ARTICLE INFO

Article history:
Received 7 May 2011
Received in revised form 7 June 2011
Accepted 8 June 2011
Available online 1 July 2011

Keywords:
Maclocycle
Riccardin
Bis(bibenzyl) natural product
S_NAr reaction

ABSTRACT

Riccardin C (RC, **1**) is a macrocyclic bis(bibenzyl) natural product exhibiting remarkable biological activity as a nuclear liver X receptors (LXRs) ligand and a lipid metabolism mediator. RC is expected to be a lead compound to develop drugs for atherosclerotic diseases, and therefore exploiting diversity-oriented synthesis of RC is a promising approach to drug discovery. In this paper, we report novel total synthesis of RC (7.4% overall yield in 16 steps) by using the intramolecular S_NAr reaction as key cyclization reaction. This is the first example of efficient macrocyclization using 3-nitro-4-fluorostilbene as an electrophile. The methodology could be applied to synthesize novel lactam analogs of RC. The diversity-oriented synthesis of RC is versatile method for the synthesis of various types of bis(bibenzyl) natural products and their derivatization.

1. Introduction

Cyclic bis(bibenzyl) natural products, produced by bryophyte, have characteristic structure and potent and diverse biological activities.[1] Riccardin C (RC, **1**, Fig. 1) is a trihydroxylated cyclic bis(-bibenzyl), isolated from the liverwort Reboulia hemisphaerica,[2] and was reported to act as a ligand for liver X receptors (LXRs).[3] LXR is a ligand-inducible transcription factor, classified in nuclear receptor superfamily, and modulates expression of ATP-binding cassette transporter (ABC) A1 and ABCG1 and cellular cholesterol efflux in THP-1 cells. Thus, LXR agonists could be potentially effective for atherosclerotic diseases, such as hyperlipidemia and diabetes.[4] Among various LXR ligands so far known, RC has unique biological activity. There are two LXR subtypes (α and β forms), and RC acted selectively as LXRα agonist, while RC suppressed the function of LXRβ as the antagonist. Therefore, RC is a lead compound for the development of novel LXR ligands as not only drug candidates for the atherosclerotic diseases but also chemical tools to investigate the physiological functions of each LXR subtype.

Cyclic bis(bibenzyl)s have been also attractive synthetic targets because of their unique structure and intrinsic difficulties of macrocyclization. Thus, several total syntheses of bis(bibenzyl)s have been reported to date.[1,5] Four total syntheses of RC have been reported previously. Nógrádi employed Wurtz coupling reaction using sodium metal in the macrocyclization step.[6] Eicher and Speicher adopted intramolecular Wittig construction of the ethylene linker between two phenolic parts (A and B rings of RC in Scheme 1) in satisfactory yield,[7] and recently Hashimoto also utilized Wittig reaction for synthesis of some RC derivatives.[8] Harrowven utilized McMurry coupling for the cyclization.[9] Recently, Fukuyama disclosed the novel total synthesis of RC utilizing

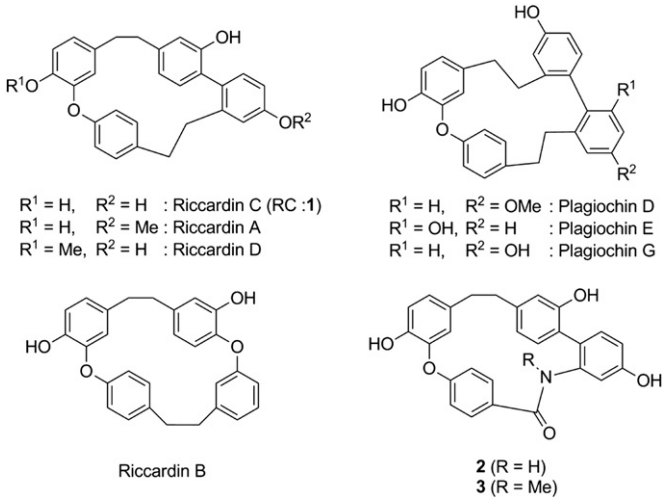
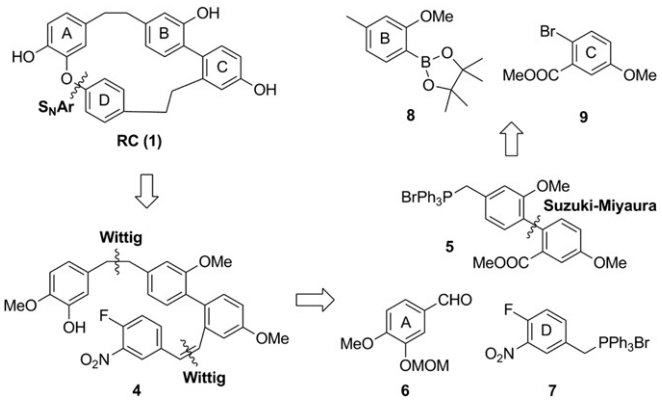


Fig. 1. Structures of Riccardin C (**1**), and related natural and synthetic derivatives.

* Corresponding author. Tel.: +81 3 5280 8032; fax: +81 3 5280 8127; e-mail address: kage.omc@tmd.ac.jp (H. Kagechika).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.06.018

Suzuki–Miyaura coupling for the construction of the macrocycle.[10] These synthetic methodologies are useful to synthesize RC itself, while these are inconvenient for development of RC analogs because of low substrate generality and applicability of the key macrocyclization step. In order to obtain a variety of macrocyclic analogs of RC, development of more concise and diversity-oriented synthetic route of RC is desirable. Herein, the novel and diversity-oriented total synthesis of RC and its application to the development of macrolactam analogs **2** and **3** are described.



Scheme 1. Retrosynthetic analysis of RC.

2. Results and discussion

2.1. Retrosynthetic analysis

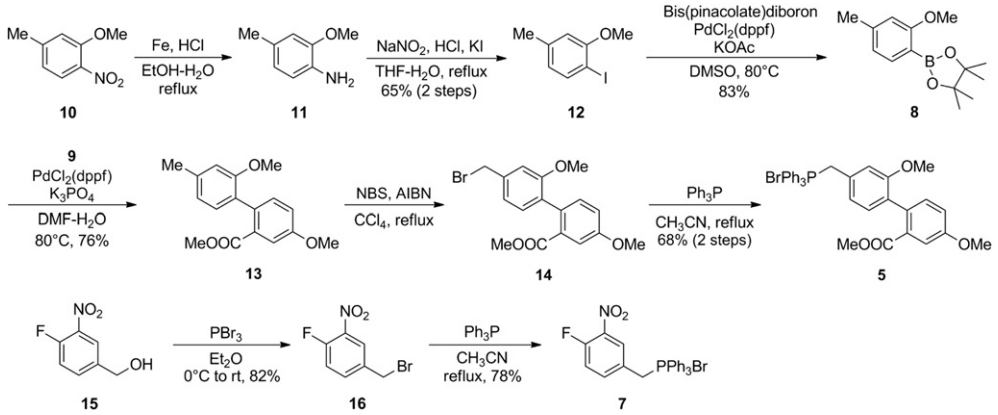
RC consists of four benzene rings (A–D rings, Scheme 1). The key step of our synthetic plan is the macrocycle construction at the diphenylether structure of A and D rings. Ullmann coupling reactions, Buchwald's palladium-catalyzed synthesis, and their variations, are popular synthetic methods of diphenylether scaffold,[11] while these methods generally need harsh conditions, such as high temperature in the presence of strong bases and metals, which sometimes troubles in purification. Considering the precedent results and the highly rigid structure of RC, use of strong base or catalyst, or elevation of reaction temperature is expected to result in unsatisfactory outcome. Classical S_NAr coupling of phenol with electron-deficient haloaryl moiety is also well utilized to construct diaryl ether, because of its mild and simple reaction conditions. Therefore, it was applied to synthesis of natural products containing diaryl ether macrocycle, such as peptide antibiotics and acetogenins.[12] The comparatively mild conditions of S_NAr reaction are desirable to synthesize not only target compound but also its derivatives bearing various functionalities. Thus, we chose S_NAr coupling reaction in the critical cyclization step for synthesis of RC. In preparation of cyclization precursor **4**, two ethylene linkers are constructed by Wittig reactions, and intermolecular Suzuki–Miyaura cross coupling was utilized in formation of B and C biphenyl moiety.

2.2. Total synthesis of RC

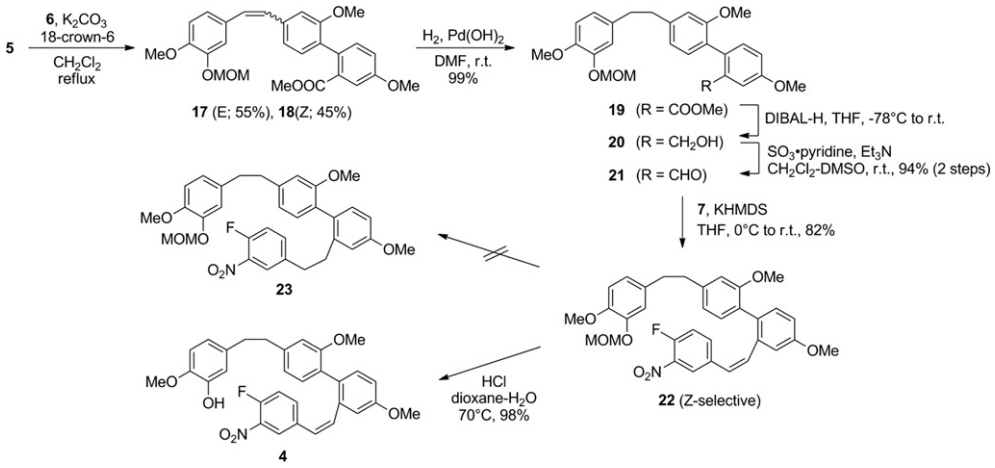
Syntheses of the B and C biphenyl fragment **5** and the D ring fragment **7** were summarized in Scheme 2. The B ring fragment **8** was prepared from 5-methyl-2-nitroanisole (**10**). Reduction of nitro group by Fe in acidic conditions, followed by Sandmeyer iodination, gave iodide **12** in 65% (two steps). Introduction of pinacolborane moiety by Miyaura–Ishiyama protocol afforded **8** in 83%.[13] Boronate **8** was coupled with commercially available C ring fragment **9** under Suzuki–Miyaura coupling conditions to afford biphenyl **13** in 76%.[14] Bromination at the benzyl position of **13** gave **14** that was reacted with triphenylphosphine gave phosphonium salt **5** in 68% (two steps). The D ring fragment **7** was prepared from benzyl alcohol **15**. Bromination of **15** using PBr_3 gave bromide **16** (82%), followed by the reaction with triphenylphosphine, gave phosphonium salt **7** in 78%.[15]

Then, the compound **4** with a bis(bibenzyl) backbone, a precursor of macrocyclization, was constructed as shown in Scheme 3. The A ring fragment **6**[16] was reacted with phosphonium salt **5** in Wittig reaction conditions using potassium carbonate as a base in the presence of 18-crown-6 to afford *E*-stilbene **17** (55%) and *Z*-stilbene **18** (45%).[17] The stereochemistry of these products was determined by ^1H NMR. The coupling constant of vinyl protons of **17** was 16.3 Hz, and this characteristic coupling constant indicated *E*-configuration. The mixture of olefins **17** and **18** were hydrogenated with $Pd(OH)_2$ in DMF gave bibenzyl **19** in quantitative yield. Reduction of ester group of **19**, and the following oxidation gave aldehyde **21** in 94% (two steps). Wittig reaction of **21** with D ring fragment **7** using KHMDS as a base in THF gave *Z*-stilbene **22** exclusively. The Wittig reaction conditions using semi-stabilized ylide generally resulted in the mixture of *E*/*Z* isomers with the ratio of near 1:1. The selective formation of *Z* isomer was preferred when the aldehyde has an aromatic substitution at the *ortho* position.[18]

In the macrocyclization, there should be some difference in reactivity between compound **22** with the *Z*-alkene linker and **23** with a more flexible alkyl linker. In order to optimize the cyclization conditions for flexible precursor **23**, compound **22** was tried to be hydrogenated. Double bonds of stilbene or cinnamate bearing



Scheme 2. Syntheses of B and C ring fragment **5** and D ring fragment **7**.



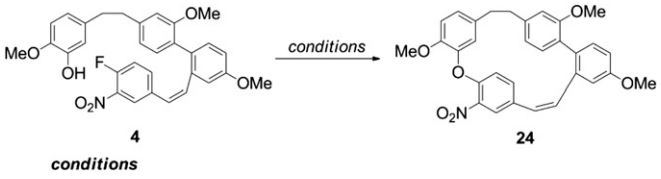
Scheme 3. Synthesis of cyclization precursor **4**.

fluoronitrophenyl moiety can be hydrogenated catalytically to alkanes by Wilkinson's catalyst.[19] However, reduction of **22** under the reported conditions did not occur. Therefore, we optimized the condition of macrocyclization using **4**, obtained by acidic treatment of **22**, as the cyclization precursor.

The results of investigation on the optimal cyclization conditions are summarized in Table 1. In previously reported intramolecular S_NAr synthesis of *ortho*-substituted diphenylether, cyclization proceeded successfully in the presence of weak bases, such as cesium fluoride or potassium carbonate at room temperature.[11,12] In the case of cyclization of **4**, the reactions using cesium fluoride or potassium carbonate were examined at ambient temperature, but the reaction did not proceed (entry 1 and 2). Cyclization reaction of **4** with stronger base, such as potassium *tert*-butoxide or sodium hydride did occur, but the yield of desired macrocyclic compound **24** was not sufficient (entry 3–5). Alternatively, the reaction using potassium carbonate at higher temperature (entry 6) or in the presence of 18-crown-6 (entry 7 and 8) improved the yield of **24**. In the result of optimization, the reaction using potassium carbonate in the presence of 0.2 equiv of 18-crown-6 at 40 °C was selected as the cyclization conditions of **4**. It is noteworthy that the result was the first successful S_NAr macrocyclization of electrophilic styrylbenzene.

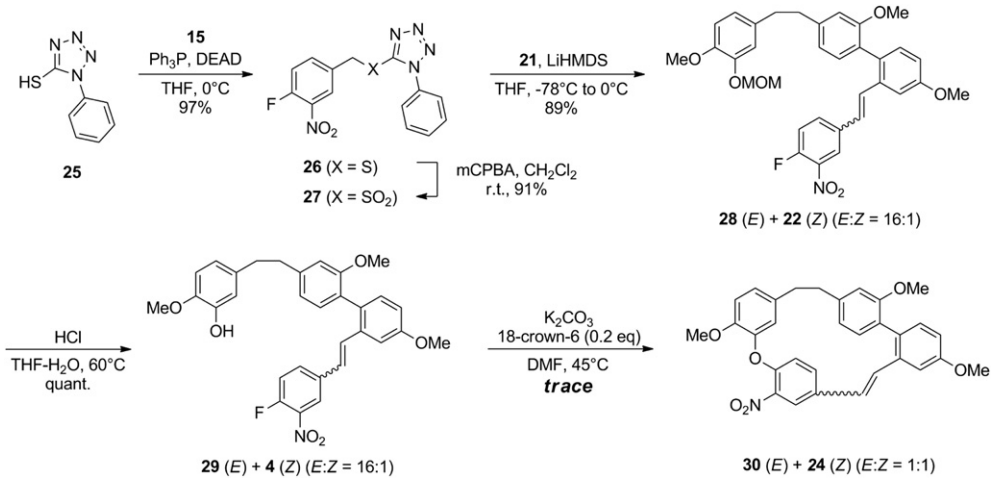
Based on the cyclization results employing the *Z*-stilbene **4** as a substrate, we examined the applicability of the conditions to *E*-stilbene substrate. The cyclization precursor with *E*-stilbene structure was prepared by Julia–Kocienski coupling reaction.[20] Mitsunobu reaction of thiol **25** and 3-fluoro-4-nitrobenzylalcohol (**15**) gave sulfide **26** in 97%, which was subsequently oxidized by *m*-CPBA to afford sulfone **27** in 91%. Julia–Kocienski coupling of **27** with aldehyde **21** gave *E*-stilbene **28**, predominantly with a small amount of *Z*-isomer **22** as byproduct, in 89% (*E*/*Z* ratio=16:1). The deprotection of MOM group gave the cyclization precursor **29** with coexistence of a trace amount of **4**. The mixture of **29** and **4** (ratio of 16:1) was subjected to the optimized cyclization conditions (Table 1, entry 8), but the desirable cyclized product was obtained only in trace amount as a mixture of 1:1 *E*/*Z* isomer. The results suggested that *Z*-configuration of the precursor was superior to *E*-isomer in the macrocyclization of bis(bibenzyl) derivatives by S_NAr reaction (Scheme 4).

Table 1
Cyclization of **4**



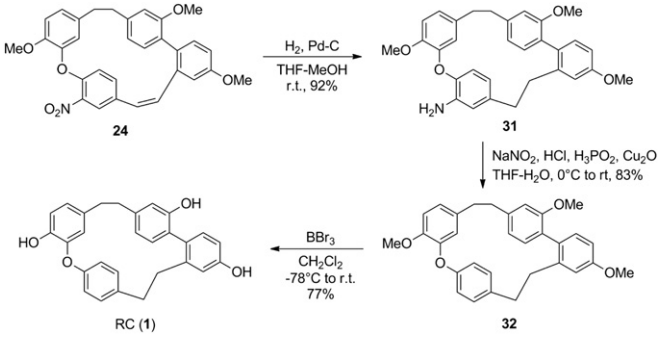
Conditions					
Entry	Base	Additive	Solvent[a]	Temp	Yield
1	CsF	—	DMF	rt	N.R.[b]
2	K_2CO_3	—	DMF	rt	N.R.[b]
3	*t*-BuOK	—	DMF	0 °C to rt	14%
4	*t*-BuOK	—	DMF	0 °C to rt	26%
5	NaH	—	CH_3CN	0 °C to rt	37%
6	K_2CO_3	—	DMF	70 °C	45%
7	K_2CO_3	18-crown-6 (0.1 equiv)	DMF	45 °C	39%
8	K_2CO_3	18-crown-6 (0.2 equiv)	DMF	40 °C	60%

[a] Concentration of **4** was 0.01 M in each condition.
[b] No reaction.



Scheme 4. Preparation and cyclization of *E*-stilbene **29**.

Macrocyclic *Z*-stilbene **24** obtained from **4** was subjected to catalytic hydrogenation gave amine **31** in 92%, and subsequent deamination via diazonium salt gave trimethyl ether of RC (**32**) in 83%. Finally, removal of three *O*-methyl groups of **32** with boron tribromide afforded RC (**1**) in 78%. Here novel total synthesis of RC was accomplished in 7.4% overall yield in 16 steps. Synthesized RC was identical to the authentic sample in ^{1}H and ^{13}C NMR spectra and HRMS (Scheme 5).



Scheme 5. Completion of total synthesis of RC (**1**).

2.3. Synthesis of novel macrolactam analogs of RC

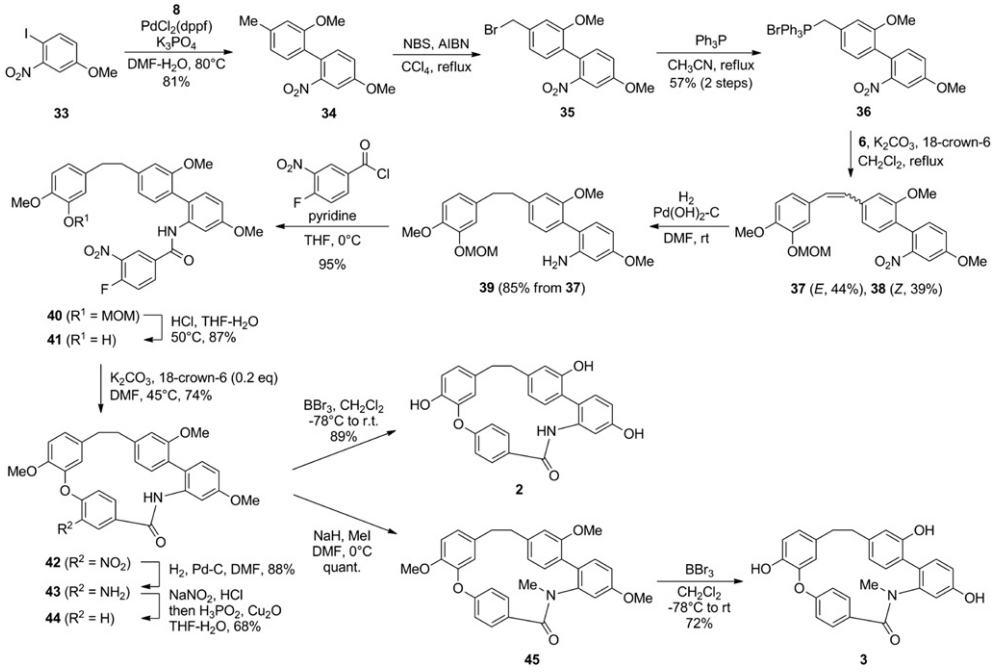
We investigated an applicability of our synthetic methodology to develop macrocyclic analogs of RC. As novel macrocyclic analogs of RC, we designed macrolactam **2** and **3** (Fig. 1). The ethylene linking group of **1** was replaced with more rigid and planar amide group, which may affect the three-dimensional structure and electronic distribution of the macrocycle, and therefore those compounds should contribute to the understanding of structure–activity relationships of bioactivity of RC.

In our preliminary investigation, formation of tetraaryl macrolactam, such as **2** and **3** by amide condensation was extremely difficult. On the bases of our results, S_NAr macrocyclization after construction of amide moiety might be superior method than macrolactamization. Therefore, we examined the synthesis of novel macrolactone analog of RC via S_NAr macrocyclization.

Synthesis of the designed macrolactams **2** and **3** was shown in Scheme 6. 4-Iodo-3-nitroanisole **33**[21] corresponding to the part of C ring was coupled with boronate **8** under Suzuki–Miyaura conditions to afford biphenyl **34** in 81%. Subsequent bromination of **34** and conversion into phosphonium salt gave **36** in 57% (two steps). Wittig reaction of **36** with **6** by using potassium carbonate as a base in the presence of 18-crown-6 gave *E*-stilbene **37** (44%) and *Z*-isomer **38** (39%). Hydrogenation of the nitro group of **37** gave amine **39** in 85%. Amide condensation of **39** with 4-fluoro-3-nitrobenzoyl chloride, followed by removal of MOM group, gave cyclization precursor **41**. The critical macrocyclization based on the optimized conditions (Table 1, entry 8) gave the cyclized compound **42** in 74%. Catalytic hydrogenation of **42** and deamination gave **44**, which was finally demethylated using boron tribromide to afford tetraaryl macrolactam **2**. N-Methylation of **44** and demethylation of three *O*-methoxy groups gave *N*-methylamide derivative **3**. Thus, the macrolactams could be obtained easily by using S_NAr reaction as key macrocyclization reaction.

2.4. Discussions

S_NAr diary ether synthesis was useful methodology to prepare RC and its analogs. In the course of total synthesis of RC, we examined S_NAr macrocyclization of three precursors, that is, *Z*-stilbene **4**, *E*-stilbene **29** and benzanilide-type substrate **41**, in which the conformational and electronic structures of bibenzyl moiety are different each other. As a result, *Z*-stilbene **4** and benzanilide **41** underwent S_NAr cyclization with sufficient yield, while *E*-stilbene **29** did not. It is interesting that benzanilide **41** underwent S_NAr macrocyclization efficiently although the predominant conformation of benzanilide part is trans, like *E*-stilbene **29**. The differences in reactivity could arise from three reasons. One is flexibility of the amide structure of **41**. The results of stilbenes suggested that conformation of the substrate with *Z*-olefinic bond is suitable for the macrocyclization of the RC type cyclic bis(bibenzyl) scaffold. Although the conformation based on *E* structure is the predominant conformation for both **29** and **41**, the rotation barrier of amide bond is lower than that of olefinic bond. Therefore, the anilide **41** could react at the reaction conditions affording the desired macrocycle **42** in sufficient yield. The second is electronic effect. The electron-withdrawing carbonyl function of the amide group increased the reactivity of the carbon atom attached to the fluorine atom toward the S_NAr cyclization. In *E*-stilbene **29**, the π-electrons of the phenyl ring will delocalize with the olefinic bond, which would decrease the reactivity. The effect will be less in *Z*-stilbene **4**, because of the twisted conformation between phenyl ring and *Z*-olefinic bond. In addition, thermodynamic stability of cyclized compounds is another reason. Macrocycle **30** with *E*-olefin substructure is thought



Scheme 6. Synthesis of novel macrolactam **2** and **3**.

to have distortion of skeletal bonds, and therefore formation of **30** would be energetically disadvantageous.

3. Conclusion

We established concise and efficient synthesis of RC in 7.4% overall yield in 16 steps. The critical ring closure was succeeded in 60% yield by intramolecular S_NAr reaction, and the requisite synthetic fragments were readily available. The novel S_NAr macrocyclization enables development of diverse RC analogs bearing various functional groups on aromatic rings and various linkers between aromatic rings. RC have unique biological activity as LXRα-specific agonist, while there is only a few studies on the structure–activity relationship, and most of them are simple chemical transformation of natural products. The concise and diversity-oriented synthesis of RC described here would provide the useful synthetic methodology in the medicinal chemistry and chemical biology research of RC and the related bis(bibenzyl)-type macrocycles.

4. Experimental section

4.1. General methods

All reagents were purchased from Sigma–Aldrich Chemical Co., Tokyo Kasei Kogyo Co, Wako Pure Chemical Industries, Kanto Kagaku Co., INC. Silica gel for column chromatography was purchased from Kanto Kagaku Co., INC. Gel permeation chromatography was conducted with LG-9201 (Japan Analytical Industry Co., Ltd., eluent: $CHCl_3$). ^1H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE 500 spectrometer. Chemical shifts for ^1H and ^{13}C NMR are reported as parts per million (ppm) relative to chloroform (7.24 ppm for ^1H NMR, 77.00 ppm for ^{13}C NMR). Mass Spectral data was collected on Bruker Daltonics microTOF-2focus or JEOL AX505H in the positive and negative ion modes. Elemental analyses were carried out by Yanaco MT-6 CHN CORDER spectrometer.

*4.1.1. 4-Iodo-3-methoxytoluene (**12**).* Iron (5.35 g, 95.7 mmol) was added to a solution of 2-nitro-5-methylanisole (10, 4.00 g, 23.9 mmol) in ethanol (60 ml) and 6 M aqueous hydrochloric acid (30 ml), and the mixture was heated at reflux for 2 h. The reaction mixture was diluted with ethyl acetate and filtrated through Celite. Evaporation of the filtrate afforded crude **11**. $NaNO_2$ (2.11 g, 30.6 mmol) was added to a solution of crude **11** (2.80 g, 20.4 mmol) in THF (80 ml) and 4 M aqueous hydrochloric acid (40 ml) at 0 °C. After 30 min, potassium iodide (4.80 g, 30.6 mmol) was added, and the mixture was heated at reflux for 3 h. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with saturated sodium thiosulfate and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ether 100:1 to 98:2) gave **12** (pale yellow oil, 3.77 g, 15.2 mmol, 65% for two steps). ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, 1H, J=7.9 Hz), 6.63 (d, 1H, J=1.2 Hz), 6.53 (dd, 1H, J=7.9, 1.2 Hz), 3.84 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.84, 139.86, 138.96, 123.36, 112.07, 81.78, 56.18, 21.42; HRMS (FAB^+) m/z 248.9780 [$(M+H)^+$: calcd for $C_8H_{10}OI$, 248.9776].

*4.1.2. (2-Methoxy-4-methylphenyl)boronic acid pinacol ester (**8**).* Compound **12** (7.44 g, 30.0 mmol) in DMSO (20 ml) was added to a suspension of bis(pinacolate)diboron (8.38 g, 33.0 mmol) and predried potassium acetate (8.84 g, 90.0 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (735 mg, 0.900 mmol) in DMSO (80 ml) under Ar atmosphere, and the mixture was stirred for 5 h at 80 °C. The reaction mixture was diluted with ethyl acetate and filtered through Celite. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 10:1) gave **8** (colorless solids, 6.19 g, 25.0 mmol, 83%). Mp 59.5–60.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, J=7.5 Hz), 6.74 (d, 1H, J=7.3 Hz), 6.65 (s, 1H), 3.80 (s, 3H), 2.33 (s, 3H), 1.32 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.39, 142.98, 136.81, 120.99, 111.44, 83.20, 55.74, 24.98, 24.77, 21.90; HRMS (FAB^+) m/z 248.1697 [$(M)^+$: calcd for $C_{14}H_{22}O_3B$, 248.1584].

*4.1.3. Methyl 2′,4-dimethoxy-4′-methylbiphenyl-2-carboxylate (**13**).* Tripotassium phosphate (9.55 g, 45.0 mmol) and

$PdCl_2(dppf)\cdot CH_2Cl_2$ (612 mg, 0.750 mmol) was added to the solution of compound **8** (3.97 g, 16.0 mmol) and methyl 2-bromo-5-methoxybenzoate (**9**) (3.68 g, 15.0 mmol) in DMF (75 ml) and water (1.5 ml) under argon atmosphere, and the mixture was stirred for 3 h at 80 °C. The reaction mixture was filtered through Celite, and diluted with water, and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 10:1) gave **13** (colorless oil, 3.25 g, 11.4 mmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 1H, J=2.8 Hz), 7.22 (d, 1H, J=8.5 Hz), 7.10 (d, 1H, J=7.5 Hz), 7.06 (dd, 1H, J=8.5, 2.8 Hz), 6.82 (dd, 1H, J=7.6, 0.6 Hz), 6.69 (s, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.51, 158.33, 155.94, 138.46, 132.52, 132.46, 131.09, 129.70, 127.33, 121.33, 117.60, 114.15, 111.13, 55.45, 55.13, 51.69, 21.62; HRMS (ESI$^+$) m/z 309.1103 [(M+Na)$^+$: calcd for $C_{17}H_{18}NaO_4$, 309.1097].

*4.1.4. [(2,4′-Dimethoxy-2′-methoxycarbonylbiphenyl-4-yl)methyl] triphenylphosphonium bromide (**5**).* *N*-Bromosuccinimide (NBS: 200 mg, 1.12 mmol) was added to a solution of **13** (388 mg, 1.36 mmol) and 2,2′-azobis(isobutyronitrile) (11.2 mg, 0.068 mmol) in CCl_4 (20 ml), and the mixture was heated at reflux. After 1 h, additional NBS (41.6 mg, 0.234 mmol) was added and refluxed for 1 h, and NBS (20.0 mg, 0.112 mmol) was further added and refluxed for another 1 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 10:1) gave bromide **14** (colorless oil, 442 mg). A solution of compound **14** (442 mg) and triphenylphosphine (317 mg, 1.21 mmol) in acetonitrile (15 ml) was heated at reflux for 14 h. The resulting white precipitates were filtrated, washed with ether, and dried in vacuo to afford **5** (colorless solids, 578.0 mg, 0.921 mmol, 68% for two steps). Mp 264.5–265.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93–7.88 (m, 3H), 7.78–7.71(m, 6H), 7.71–7.64 (m, 6H), 7.32 (d, 1H, J=2.7 Hz), 7.16 (d, 1H, J=8.5 Hz), 7.11 (dd, 1H, J=8.5, 2.8 Hz), 7.04 (dd, 1H, J=7.7, 0.7 Hz), 6.69 (m, 1H), 6.47 (m, 1H), 4.93 (d, 2H, J=14.7 Hz), 3.83 (s, 3H), 3.65 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.64, 160.31, 157.84, 136.45 (d, J=2.8 Hz), 135.61 (d, J=9.5 Hz), 133.81, 133.42, 132.48, 131.40 (d, J=12.5 Hz), 128.67 (d, J=9.1 Hz), 124.55 (d, J=6.0 Hz), 119.53, 118.84, 118.22, 115.64, 114.25 (d, J=4.8 Hz), 56.04, 55.58, 52.39, 31.20 (d, J=47.8 Hz); HRMS (ESI$^+$) m/z 547.2039 [(M+H)$^+$: calcd for $C_{35}H_{32}O_4P$, 547.2038].

*4.1.5. 4-Fluoro-3-nitrobenzyl bromide (**16**).* A solution of 4-fluoro-3-nitrobenzylalcohol (3.04 g, 17.8 mmol) in ether (20 ml) was added dropwise to a solution of phosphorus tribromide (1.92 g, 7.11 mmol) in ether (80 ml) at 0 °C, and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was washed with saturated aqueous sodium bicarbonate and brine, dried with sodium sulfate, and evaporated to afford **16** (pale yellow solids, 3.41 g, 14.6 mmol, 82%). Mp 55.5–56.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, 1H, J=6.9, 2.3 Hz), 7.66 (ddd, 1H, J=8.6, 4.1, 2.4 Hz), 7.27 (dd, 1H, J=10.4, 8.6 Hz), 4.47 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.09 (d, J=266.7 Hz), 135.98 (d, J=8.9 Hz), 134.98 (d, J=4.3 Hz), 126.47, 126.46 (d, J=2.2 Hz), 119.00 (d, J=22.1 Hz), 30.22; HRMS (EI+) m/z 232.9494 [(M+H)$^+$: calcd for $C_7H_5NO_2BrF$, 232.9488].

*4.1.6. 4-Fluoro-3-nitrobenzyltriphenylphosphonium bromide (**7**).* A solution of compound **16** (3.41 g, 14.6 mmol) and triphenylphosphine (3.82 g, 14.6 mmol) in acetonitrile (40 ml) was heated at reflux for 1 day. The resulting white precipitates were collected and washed with ether, and dried in vacuo to afford **7** (colorless solids, 5.67 g, 11.4 mmol, 78%). Mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95–7.89 (m, 3H), 7.79–7.68 (m, 13H), 7.55–7.46 (m, 2H), 5.43 (d, J=15.7 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.54 (d, J=261.3 Hz), 138.52 (d, J=6.9 Hz), 136.29, 135.26 (d, 3C, J=2.6 Hz), 134.08 (d, 6C, J=10.0 Hz), 130.20 (d, 6C, J=12.5 Hz), 128.25, 125.59 (d, J=4.2 Hz), 119.25 (d, J=18.6 Hz), 117.03 (d, 3C, J=85.9 Hz), 26.96 (d, J=45.3 Hz); HRMS (ESI$^+$) m/z 416.1211 [(M+H)$^+$: calcd for $C_{25}H_{20}FNO_2P$, 416.1210].

*4.1.7. Methyl 2′,4-dimethoxy-4′-[4-methoxy-3-(methoxymethoxy) styryl]biphenyl-2-carboxylate [**17** (E isomer) and **18** (Z isomer)].* Potassium carbonate (464 mg, 3.35 mmol) and 18-crown-6 (59.2 mg, 0.224 mmol) was added to a solution of **5** (1.40 g, 2.24 mmol) and **6** (526 mg, 2.68 mmol) in methylene chloride (30 ml), and the mixture was heated at reflux for 2 days. The reaction mixture was evaporated and dissolved in THF (30 ml) and MeOH (30 ml), and $NaBH_4$ (60.0 mg) was added the mixture at 0 °C, and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into 2 M aqueous hydrochloric acid at 0 °C and diluted with ethyl acetate. The organic layer was washed with 2 M aqueous hydrochloric acid and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 3:1 to 7:3) gave **17** (colorless oil, 605 mg, 1.30 mmol, 55%) and **18** (colorless oil, 491 mg, 1.06 mmol, 45%). Compound **17**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, 1H, J=2.8 Hz), 7.36 (d, 1H, J=2.1 Hz), 7.25 (d, 1H, J=8.7 Hz), 7.19 (d, 1H, J=7.7 Hz), 7.14 (dd, 1H, J=7.7, 1.3 Hz), 7.13 (dd, 1H, J=8.4, 2.1 Hz), 7.06 (dd, 1H, J=8.5, 2.8 Hz), 7.04 (d, 1H, J=16.3 Hz), 7.01–6.98 (m, 2H), 6.97 (d, 1H, J=16.3 Hz), 6.88 (d, 1H, J=8.4 Hz), 5.28 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.57, 158.51, 156.34, 149.57, 146.76, 137.99, 132.56, 132.43, 130.72, 130.63, 130.11, 129.56, 128.14, 127.02, 121.16, 119.19, 117.67, 114.23, 114.06, 111.81, 107.73, 95.57, 56.26, 55.99, 55.49, 55.23, 51.74; HRMS (FAB$^+$) m/z 464.1841 [(M)$^+$: calcd for $C_{27}H_{28}O_7$, 464.1835]. Compound **18**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, 1H, J=2.8 Hz), 7.22 (d, 1H, J=8.5 Hz), 7.12 (d, 1H, J=2.1 Hz), 7.10 (d, 1H, J=7.7 Hz), 7.05 (dd, 1H, J=8.5, 2.8 Hz), 6.96–6.92 (m, 2H), 6.78 (d, 1H, J=1.4 Hz), 6.76 (d, 1H, J=8.4 Hz), 6.52 (s, 2H), 5.08 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.64 (s, 3H), 3.51 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.52, 158.47, 155.77, 149.10, 146.00, 137.69, 132.59, 132.39, 130.74, 130.20, 129.72 (2C), 129.16, 129.08, 123.41, 121.50, 117.63, 117.47, 114.17, 111.40, 110.52, 95.55, 56.08, 55.87, 55.47, 54.97, 51.66; HRMS (FAB$^+$) m/z 464.1819 [(M)$^+$: calcd for $C_{27}H_{28}O_7$, 464.1835].

*4.1.8. Methyl 2′,4-dimethoxy-4′-[4-methoxy-3-(methoxymethoxy) phenethyl]biphenyl-2-carboxylate (**19**).* $Pd(OH)_2$ on carbon (10%, 2.0 mg) was added to a solution of **17** and **18** (10.5 mg, 0.226 mmol) in DMF (1.5 ml). The reaction mixture was stirred for 20 h under hydrogen atmosphere at room temperature, and filtered through Celite. The filtrate was poured into ethyl acetate and water. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 2:1) gave **19** (colorless oil, 10.4 mg, 0.223 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, 1H, J=2.7 Hz), 7.23 (d, 1H, J=8.5 Hz), 7.12 (d, 1H, J=7.6 Hz), 7.06 (dd, 1H, J=8.5, 2.8 Hz), 7.01 (br s), 6.84 (dd, 1H, J=7.6, 1.5 Hz), 6.81 (m, 2H), 6.65 (d, 1H, J=1.3 Hz), 5.20 (s, 2H), 3.85 (s, 6H), 3.66 (s, 3H), 3.63 (s, 3H), 3.51 (s, 3H), 2.94–2.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.55, 158.35, 155.96, 148.03, 146.33, 142.33, 134.57, 132.50, 130.99, 129.76, 127.82, 122.14, 120.67, 117.61, 116.92, 114.13, 111.75, 110.51, 95.59, 56.17, 55.97, 55.45, 51.66, 38.15, 37.12. HRMS (ESI$^+$) m/z 489.1892 [(M+Na)$^+$: calcd for $C_{27}H_{30}NaO_7$, 489.1884].

*4.1.9. 2-Hydroxymethyl-2′,4-dimethoxy-4′-[4-methoxy-3-(methoxymethoxy)phenethyl]biphenyl (**20**).* Diisobutylaluminium hydride (1.02 M in *n*-hexane, 3.68 ml, 3.75 mmol) was added to a solution of **19** (700 mg, 1.50 mmol) in THF (20 ml) at −78 °C under Ar atmosphere, and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was poured into 2 M aqueous hydrochloric acid at 0 °C, and diluted with ethyl acetate. The organic layer was washed with 2 M aqueous hydrochloric acid and brine, dried with

sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 2:1 to 1:1) gave **20** (colorless oil, 671 mg, 1.53 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, 1H, *J*=7.5 Hz), 7.09 (d, 1H, *J*=3.0 Hz), 7.03 (d, 1H, *J*=7.6 Hz), 6.98 (d, 1H, *J*=1.3 Hz), 6.88 (dd, 1H, *J*=8.3, 2.7 Hz), 6.84 (dd, 1H, *J*=7.6, 1.5 Hz), 6.83–6.79 (m, 2H), 6.73 (d, 1H, *J*=1.4 Hz), 5.20 (s, 2H), 4.39 (d, 2H, *J*=15.6 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (s, 3H), 3.51(s, 3H), 2.95–2.86 (m, 4H), 2.20 (t, 1H, *J*=6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.22, 156.40, 148.09, 146.35, 142.79, 140.77, 134.40, 131.43, 131.34, 129.69, 127.11, 122.16, 121.04, 116.94, 113.39, 113.32, 111.80, 111.45, 95.59, 63.83, 56.17, 55.98, 55.70, 55.27, 38.12, 37.17; HRMS (ESI$^+$) *m*/*z* 461.1939 [(M+Na)$^+$: calcd for $C_{26}H_{30}NaO_6$, 461.1935].

*4.1.10. 2′,4-Dimethoxy-4′-[4-methoxy-3-(methoxymethoxy)phenethyl]biphenyl-2-aldehyde (**21**).* Sulfur trioxide-pyridine complex (1.46 g, 9.19 mmol) was added to a solution of **20** (671 mg, 1.53 mmol) in methylene chloride (20 ml) and DMSO (4.0 ml) and distilled triethylaminde (2.0 ml, 14.7 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. 2 M aqueous sodium hydroxide was added at 0 °C and, the mixture was stirred for 30 min. The organic layer was washed with 2 M aqueous sodium hydroxide, 2 M aqueous hydrochloric acid and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate=2:1) gave **21** (colorless oil, 614 mg, 1.41 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.47 (d, 1H, *J*=2.8 Hz), 7.26 (d, 1H, *J*=8.5 Hz), 7.17 (dd, 1H, *J*=8.4, 2.8 Hz), 7.14 (d, 1H, *J*=7.5 Hz), 6.99 (d, 1H, *J*=1.7 Hz), 6.87 (dd, 1H, *J*=7.6, 1.5 Hz), 6.82 (d, 1H, *J*=8.2 Hz), 6.79 (dd, 1H, *J*=8.2, 1.8 Hz), 6.71 (d, 1H, *J*=0.8 Hz), 5.20 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.68 (s, 3H), 3.50 (s, 3H), 2.99–2.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.64, 159.04, 156.48, 148.12, 146.40, 143.78, 134.87, 134.72, 134.28, 132.51, 131.43, 124.09, 122.18, 121.21, 121.01, 116.90, 111.78, 111.02, 109.33, 95.60, 56.19, 56.00, 55.53, 55.34, 38.18, 37.14. HRMS (ESI$^+$) *m*/*z* 459.1789 [(M+Na)$^+$: calcd for $C_{26}H_{28}NaO_6$, 459.1778].

*4.1.11. (Z)-2-(4-Fluoro-3-nitrostyryl)-2′,4-dimethoxy-4′-[4-methoxy-3-(methoxymethoxy)phenethyl]biphenyl (**22**).* KHMDS (0.5 M in toluene, 9.20 ml, 4.60 mmol) was added to a suspension of **7** (1.90 g, 3.83 mmol) in THF (15 ml) at 0 °C under argon atmosphere, and the mixture was stirred for 30 min at ambient temperature. A solution of **21** (614 mg, 1.32 mmol) in THF (5.0 ml) was added to the reaction vessel at 0 °C and, the mixture was stirred for 1 day at room temperature. The reaction mixture was poured into 2 M aqueous hydrochloric acid and ethyl acetate. The organic layer was washed with 2 M aqueous hydrochloric acid and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 4:1 to 3:1) gave **22** (orange oil, 619 mg, 1.08 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.23 (dd, 1H, *J*=8.6, 2.3 Hz), 8.13–8.08 (m, 1H), 7.80 (s, 1H), 7.35 (dd, 1H, *J*=10.0, 8.8 Hz), 7.20 (d, 1H, *J*=8.5 Hz), 7.14 (d, 1H, *J*=8.2 Hz), 6.95–6.90 (m, 3H), 6.84–6.79 (m, 3H), 5.13 (s, 2H), 3.87 (s, 6H), 3.83 (s, 3H), 3.45 (s, 3H), 2.99–2.93 (m, 3H), 2.93–2.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.46, 159.57, 157.27 (d, *J*=271.0 Hz), 155.33, 148.10, 146.29, 143.94, 136.80 (d, *J*=7.5 Hz), 135.73, 135.02 (d, *J*=9.4 Hz), 134.12, 132.37, 132.00 (d, *J*=4.1 Hz), 131.76, 124.60, 124.08, 123.09, 122.40, 122.12, 119.20 (d, *J*=21.5 Hz), 116.99, 112.36, 111.86, 111.77, 107.55, 95.48, 56.43, 56.07, 55.95, 55.43, 37.92, 36.94. HRMS (ESI$^+$) *m*/*z* 596.2057 [(M+Na)$^+$: calcd for $C_{33}H_{32}FNNaO_7$, 596.2055].

*4.1.12. (Z)-2-(4-Fluoro-3-nitrostyryl)-2′,4-dimethoxy-4′-(3-hydroxy-4-methoxyphenethyl)biphenyl (**4**).* A solution of **22** (64.9 mg, 0.113 mmol) in 1,4-dioxane (2.0 ml) and 4 M aqueous hydrochloric acid (2.0 ml) was stirred for 3 h at 70 °C. The reaction mixture was poured into ethyl acetate and water. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 4:1) gave **4** (orange oil, 58.7 mg, 0.111 mmol, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, 1H, *J*=7.1, 2.2 Hz), 7.39 (ddd, 1H, *J*=8.4, 4.2, 1.8 Hz), 7.21 (d, 1H, *J*=8.5 Hz), 7.02 (dd, 1H, *J*=10.6, 8.7 Hz), 6.92 (d, 1H, *J*=7.5 Hz), 6.86 (dd, 1H, *J*=8.5, 2.7 Hz), 6.78 (d, 1H, *J*=2.1 Hz), 6.77 (d, 1H, *J*=8.2 Hz), 6.74 (dd, 1H, *J*=8.6, 1.5 Hz), 6.69 (d, 1H, *J*=2.8 Hz), 6.67 (dd, 1H, *J*=8.2, 2.1 Hz), 6.65 (d, 1H, *J*=1.3 Hz), 6.51 (d, 1H, *J*=12.0 Hz), 6.29 (d, 1H, *J*=12.0 Hz), 5.58 (s, 2H), 3.86 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 2.92–2.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.57, 156.63, 153.98 (d, *J*=257.5 Hz), 145.47, 144.86, 142.76, 137.08, 136.81, 135.55 (d, *J*=8.3 Hz), 135.07, 134.34 (d, *J*=3.6 Hz), 133.39, 132.03, 130.84, 130.77, 127.00, 126.10, 125.78, 120.32, 119.73, 117.70 (d, *J*=21.0 Hz), 114.71, 113.98, 113.43, 110.98, 110.61, 56.01, 55.25, 55.07, 38.05, 37.08; HRMS (ESI$^+$) *m*/*z* 552.1800 [(M+Na)$^+$: calcd for $C_{31}H_{28}FNNaO_6$, 552.1793].

*4.1.13. (Z)-Macrocyclic ether **24** (Table 1. entry 8).* Potassium carbonate (138 mg, 1.00 mmol) and 18-crown-6 (21.2 mg, 0.080 mmol) was added to a solution of **4** (212 mg, 0.400 mmol) in DMF (40 ml), and the mixture was stirred for 2 h at 40 °C. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 6:1) gave **24** (pale yellow oil, 116 mg, 0.242 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): Two conformers were observed. δ 7.69 (d, 1H (major), *J*=2.2 Hz), 7.66 (d, 1H (minor), *J*=2.2 Hz), 7.31 (br d, 1H (major), *J*=8.6 Hz), 7.28 (dd, 1H (minor), *J*=8.4, 1.8 Hz), 7.23–7.19 (m, 1H), 6.97 (d, 1H, *J*=7.7 Hz), 6.93–6.80 (m, 5H), 6.77 (d, 1H, *J*=7.7 Hz), 6.38–6.22 (m, 3H), 5.22 (d, 1H (major), *J*=2.3 Hz), 5.14 (d, 1H (minor), *J*=8.4 Hz), 3.94 (s, 3H (major)), 3.93 (s, 3H (minor)), 3.86 (s, 3H), 3.63 (s, 3H (major)), 3.62 (s, 3H (minor)), 2.90–2.68 (m, 4H); HRMS (ESI$^+$) *m*/*z* 532.1738 [(M+Na)$^+$: calcd for $C_{31}H_{27}NNaO_6$, 532.1731].

*4.1.14. 5-(4-Fluoro-3-nitrobenzylthio)-1-phenyltetrazole (**26**).* Diethyl azodicarboxylate (2.2 M in toluene, 1.82 ml, 4.00 mmol) was added to a mixture of 4-fluoro-3-nitrobenzylalcohol **15** (513 mg, 3.00 mmol), 5-mercapto-1-phenyltetrazole **25** (535 mg, 3.30 mmol), and triphenylphosphine (1.41 g, 4.00 mmol) in THF (15 ml) at 0 °C under argon atmosphere, and the mixture was stirred for 3 h at 0 °C. After evaporation, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 7:3) to afford **26** (963 mg, 2.91 mmol, 97%) as yellow solids. Mp 127.5–128.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, 1H, *J*=6.8, 2.3 Hz), 7.79 (ddd, 1H, *J*=8.5, 4.1, 2.4 Hz), 7.57–7.47 (m, 5H), 7.23 (dd, 1H, *J*=10.5, 8.6 Hz), 4.60 (s, 2H); HRMS (FAB$^+$) *m*/*z* 332.0627 [(M+H)$^+$: calcd for $C_{14}H_{11}FN_5O_2S$, 332.0617].

*4.1.15. 5-(4-Fluoro-3-nitrobenzylsulfonyl)-1-phenyltetrazole (**27**).* *m*-Chloroperbenzoic acid (77%, 672 mg, 3.00 mmol) was added to a solution of **26** (166 mg, 0.500 mmol) in methylene chloride (10 ml), and the mixture was stirred for 1 day at ambient temperature. The reaction mixture was poured into saturated sodium thiosulfate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 7:3) to afford **27** (165 mg, 0.454 mmol, 91%) as yellow solids. Mp 132.5–133.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, 1H, *J*=6.8, 2.2 Hz), 7.77 (ddd, 1H, *J*=8.6, 4.0, 2.4 Hz), 7.65–7.53 (m, 5H), 7.31 (dd, 1H, *J*=10.1, 9.2 Hz), 5.05 (s, 2H); HRMS (FAB$^+$) *m*/*z* 364.0520 [(M+H)$^+$: calcd for $C_{14}H_{11}FN_5O_4S$, 364.0520].

*4.1.16. (E)-2-(4-Fluoro-3-nitrostyryl)-2′,4-dimethoxy-4′-[4-methoxy-3-(methoxymethoxy)phenethyl]biphenyl (**28**).* LiHMDS (1.0 M in toluene, 0.46 ml, 0.46 mmol) was added to a solution of **27**

(152 mg, 0.418 mmol) in THF (2 ml) at −78 °C under argon atmosphere, and the mixture was stirred for 30 min at 0 °C. Thereafter, a solution of **21** (91.3 mg, 0.209 mmol) in THF (1.0 ml) was added dropwise to the mixture at −78 °C, and the mixture was stirred for 3 h at 0 °C. The reaction mixture was poured into saturated aqueous ammonium chloride, and diluted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 7:3) and following gel permeation chromatography gave a mixture of **28** and **21** (106 mg, 0.185 mmol, 97%) as yellow oil in a ratio of 16:1. **28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, 1H, *J*=7.0, 2.3 Hz), 7.52 (ddd, 1H, *J*=8.6, 4.1, 2.3 Hz), 7.23 (d, 1H, *J*=1.6 Hz), 7.22 (d, 1H, *J*=8.6 Hz), 7.19 (dd, 1H, *J*=10.5, 8.7 Hz), 7.06 (d, 1H, *J*=7.5 Hz), 7.02 (d, 1H, *J*=1.7 Hz), 6.94 (s, 2H), 6.92 (dd, 1H, *J*=8.5, 2.7 Hz), 6.86 (dd, 1H, *J*=7.6, 1.5 Hz), 6.85 (dd, 1H, *J*=8.2, 1.8 Hz), 6.83 (d, 1H, *J*=8.2 Hz), 6.78 (d, 1H, *J*=1.3 Hz), 5.20 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.69 (s, 3H), 3.50 (s, 3H), 2.99–2.90 (m, 4H); HRMS (FAB$^+$) *m*/*z* 574.2249 [(M+H)$^+$: calcd for $C_{33}H_{32}FNO_7$, 574.2241].

*4.1.17. (E)-2-(4-Fluoro-3-nitrostyryl)-2′,4-dimethoxy-4′-(3-hydroxy-4-methoxyphenethyl)biphenyl (**29**).* A mixture of **28** and **21** (16:1, 78.3 mg, 0.137 mmol) in THF (3.0 ml) and 4 M aqueous hydrochloric acid (2.5 ml) was stirred for 3 h at 50 °C. The reaction mixture was poured into ethyl acetate and brine, and the organic layer was washed with brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 3:1) gave **29** (pale yellow oil, 75.4 mg, 0.142 mmol, quant.) as a mixture of **21** and **4** (16:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, 1H, *J*=7.0, 2.2 Hz), 7.55 (ddd, 1H, *J*=8.7, 4.1, 2.3 Hz), 7.26–7.23 (m, 3H), 7.19 (dd, 1H, *J*=10.5, 8.6 Hz), 7.07 (d, 1H, *J*=7.5 Hz), 6.95 (s, 2H), 6.94 (dd, 1H, *J*=8.4, 2.6 Hz), 6.87 (dd, 1H, *J*=8.1, 1.2 Hz), 6.82–6.77 (m, 2H), 6.71 (dd, 1H, *J*=8.2, 2.0 Hz), 5.68 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.70 (s, 3H), 3.02–2.87 (m, 4H); HRMS (FAB$^+$) *m*/*z* 530.1972 [(M+H)$^+$: calcd for $C_{31}H_{29}FNO_6$, 530.1979].

*4.1.18. (E)-Macrocyclic ether **30**.* Potassium carbonate (6.9 mg, 0.050 mmol) and 18-crown-6 (1.1 mg, 0.004 mmol) was added to a solution of **21** and **2** (16:1, 10.6 mg, 0.020 mmol) in DMF (2.0 ml), and the mixture was stirred for 2 h at 45 °C. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate 6:1) gave a mixture of **30** and **24** (pale yellow oil, 0.2 mg, 0.40 μmol, 2%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, 1H (major), *J*=2.1 Hz), 7.73 (d, 1H (minor), *J*=2.1 Hz), 7.36 (dd, 1H (minor), *J*=8.6, 2.0 Hz), 7.30 (dd, 1H (major), *J*=8.6, 2.0 Hz), 7.27–6.77 (m, 8H), 6.66 (d, 1H (major), *J*=7.6 Hz), 6.60 (d, 1H (minor), *J*=7.6 Hz), 6.60–6.56 (m, 1H), 6.47 (s, 1H (major)), 6.38 (s, 1H (minor)), 6.16 (d, 1H (major), *J*=16.1 Hz), 6.04 (d, 1H (minor), *J*=16.1 Hz), 5.70 (d, 1H (minor), *J*=1.8 Hz), 5.63 (d, 1H (major), *J*=1.8 Hz), 3.94 (s, 3H (major)), 3.93 (s, 3H (minor)), 3.87 (s, 3H), 3.69 (s, 3H (major)), 3.64 (s, 3H (minor)), 3.04–2.65 (m, 4H).

*4.1.19. Macrocyclic amine **31**.* Palladium on carbon (10%, 5.0 mg) was added to a solution of 24 (17.9 mg, 0.035 mmol) in THF (0.5 ml) and MeOH (1.0 ml), and the mixture was stirred for 2 h under hydrogen atmosphere. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 6:1) to give **23** (colorless oil, 15.5 mg, 0.032 mmol, 92%). ^{1}H NMR (500 MHz, 453 K, DMSO-d_6) δ 6.95 (d, 1H, *J*=8.2 Hz), 6.92 (d, 1H, *J*=2.7 Hz), 6.92 (d, 1H, *J*=8.4 Hz), 6.80 (d, 1H, *J*=7.5 Hz), 6.80 (m, 1H), 6.77 (dd, 1H, *J*=8.4, 2.7 Hz), 6.57 (d, 1H, *J*=1.2 Hz), 6.47 (d, 1H, *J*=8.0 Hz), 6.26 (dd, 1H, *J*=7.6, 1.3 Hz), 6.24 (d, 1H, *J*=2.0 Hz), 6.09 (dd, 1H, *J*=8.0, 2.0 Hz), 5.81 (d, 1H, *J*=2.0 Hz), 3.88 (s, 3H), 3.84 (s, 3H), 3.61 (s, 3H), 2.84–2.77 (m, 8H); HRMS (ESI$^+$) *m*/*z* 504.2143 [(M+Na)$^+$: calcd for $C_{31}H_{31}NNaO_4$, 504.2145].

*4.1.20. Riccardin C trimethyl ether (**32**).* Aqueous hydrochloric acid (4 M, 1.2 ml) was added to a solution of **31** (52.9 mg, 0.110 mmol) in THF (4.0 ml) at 0 °C, and the mixture was stirred for 15 min at ambient temperature. A solution of $NaNO_2$ (22.8 mg, 0.330 mmol) in water (0.5 ml) was added to the mixture at 0 °C, and the mixture was stirred for 1 h at 0 °C. Then, 30% H_3PO_2 (242 mg, 1.10 mmol) and Cu_2O (15.7 mg, 0.110 mmol) were added to the mixture, and the mixture was stirred for 10 min at 0 °C, then 4 h at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 6:1) to give **32** (colorless oil, 42.5 mg, 0.091 mmol, 83%). ^{1}H NMR (500 MHz, $CDCl_3$, 353 K) δ 6.94 (d, 1H, *J*=8.5 Hz), 6.91 (d, 1H, *J*=2.7 Hz), 6.86 (d, 1H, *J*=8.2 Hz), 6.78 (d, 1H, *J*=7.6 Hz), 6.76 (d, 2H, *J*=8.8 Hz), 6.73 (dd, 1H, *J*=8.5, 2.7 Hz), 6.71 (dd, 1H, *J*=8.3, 2.0 Hz), 6.63 (d, 2H, *J*=8.6 Hz), 6.45 (d, 1H, *J*=1.5 Hz), 6.24 (dd, 1H, *J*=7.6, 1.5 Hz), 5.53 (d, 1H, *J*=2.1 Hz), 3.83 (s, 3H), 3.81 (s, 3H), 3.58 (s, 3H), 2.91–2.84 (m, 4H), 2.78–2.67 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.11, 155.96, 152.72, 148.64, 146.89, 143.24, 141.20, 139.69, 133.77, 132.42, 132.39, 130.90, 129.54, 127.57, 122.29, 121.68, 121.38, 116.64, 115.36, 111.78, 111.41, 111.14, 56.09, 55.21, 55.19, 38.22, 38.07, 37.23, 35.57; HRMS (ESI$^+$) *m*/*z* 489.2048 [(M+Na)$^+$: calcd for $C_{31}H_{30}NaO_4$, 489.2036].

*4.1.21. Riccardin C (**1**).* BBr_3 (1.0 M in CH_2Cl_2, 0.240 ml, 0.240 mmol) was added to a solution of **32** (18.7 mg, 0.040 mmol) in methylene chloride (2.0 ml) at −78 °C and, the mixture was stirred for 2 h at room temperature. The reaction was poured into methanol at 0 °C, and diluted with methylene chloride. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 3:2) to give **1** (colorless solids, 13.0 mg, 0.031 mmol, 77%). Mp 192.5–193.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, 1H, *J*=8.3 Hz), 6.95 (d, 1H, *J*=2.6 Hz), 6.90 (d, 1H, *J*=8.1 Hz), 6.89–6.73 (m, 2H), 6.79–6.75 (m, 1H), 6.76 (d, 2H, *J*=7.7 Hz), 6.72 (dd, 1H, *J*=8.1, 1.9 Hz), 6.37 (d, 1H, *J*=1.5 Hz), 6.21 (dd, 1H, *J*=7.7, 1.6 Hz), 5.62 (br s, 1H), 5.34 (d, 1H, *J*=2.1 Hz), 5.14 (br s, 1H), 4.80 (br s, 1H), 3.07–2.99 (m, 1H), 2.92–2.82 (m, 2H), 2.80–2.58 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.89, 152.56, 151.81, 146.28, 143.76, 143.29, 141.95, 139.80, 133.10, 132.84, 131.37, 129.33, 128.25, 124.38, 122.35, 122.16, 121.68, 117.47, 116.04, 116.03, 114.92, 114.29, 38.08, 37.73, 37.02, 34.95; HRMS (ESI$^+$) *m*/*z* 447.1567 [(M+H)$^+$: calcd for $C_{28}H_{24}NaO_4$, 447.1572].

*4.1.22. 2′,4-Dimethoxy-4′-methyl-2-nitrobiphenyl (**34**).* K_3PO_4 (5.09 g, 24.0 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (327 mg, 0.400 mmol) was added to a solution of 4-iodo-3-nitroanisole (**33**, 2.28 g, 8.00 mmol) and **8** (2.18 g, 8.80 mmol) in DMF (30 ml) and water (0.6 ml) under argon atmosphere, and the mixture was stirred for 3 h at 70 °C. The reaction mixture was filtered through Celite, and the filtrate was diluted with water, extracted with methylene chloride. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 15:1 to 10:1) to give **34** (orange solid, 1.78 g, 6.52 mmol, 81%). Mp 137.5–138.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 1H, *J*=2.6 Hz), 7.28 (d, 1H, *J*=8.5 Hz), 7.15 (d, 1H, *J*=7.7 Hz), 7.14 (dd, 1H, *J*=8.5, 2.7 Hz), 6.87 (d, 1H, *J*=7.6 Hz), 6.71 (s, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.81, 155.73, 150.04, 139.58, 133.23, 129.35, 125.19, 123.94, 121.76, 118.85, 111.55, 108.94,

55.78, 55.00, 21.61; HRMS (FAB$^+$) m/z 274.1075 [(M+H)$^+$: calcd for $C_{15}H_{16}NO_4$, 274.1079].

*4.1.23. [(2,4′-Dimethoxy-2′-nitrobiphenyl-4-yl)methyl]triphenylphosphonium bromide (**36**).* Compound **36** was prepared from **34** (1.36 g, 5.00 mmol) according to the synthetic procedure for **5** from **13**. Compound **36**: yellow solids, 1.75 g, 2.85 mmol, 57% (two steps); mp 277.5–278.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78–7.69 (m, 9H), 7.64–7.58 (m, 6H), 7.38 (d, 1H, J=2.6 Hz), 7.07 (d, 1H, J=8.5 Hz), 7.01 (dd, 1H, J=8.5, 2.6 Hz), 6.89 (d, 1H, J=7.6 Hz), 6.89 (d, 1H, J=7.6 Hz), 6.85 (t, 1H, J=1.9 Hz), 6.76 (ddd, 1H, J=7.5, 2.7, 1.6 Hz), 5.52 (d, 2H, J=13.8 Hz), 3.83 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.14, 155.92, 149.93, 134.75 (d, 6C, J=2.9 Hz), 134.66, 133.11, 130.06 (d, 6C, J=11.6 Hz), 129.52 (d, J=3.8 Hz), 128.76 (d, J=8.6 Hz), 126.98 (d, J=4.6 Hz), 124.62, 123.69 (d, J=5.6 Hz), 118.71, 117.94 (d, J=85.7 Hz), 114.90 (d, J=5.2 Hz), 109.29, 55.83, 55.49, 30.72 (d, J=46.3 Hz); HRMS (FAB$^+$) m/z 534.1848 [(M−Br$^-$)$^+$: calcd for $C_{33}H_{29}NO_4P$, 534.1834].

*4.1.24. 2′,4-Dimethoxy-4′-[4-methoxy-3-(methoxymethoxy)styryl]-2-nitrobiphenyl [**37** (E isomer) and **38** (Z isomer)].* Compounds **37** and **38** were prepared from **36** (1.61 g, 2.63 mmol) and **6** (491 mg, 2.50 mmol) according to the synthetic procedure for **17** and **18** from **5**. Compound **37**: yellow oil, 499 mg, 1.11 mmol, 44%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, 1H, J=2.7 Hz), 7.35 (d, 1H, J=2.0 Hz), 7.29 (d, 1H, J=8.5 Hz), 7.23 (d, 1H, J=7.8 Hz), 7.16 (dd, 1H, J=7.8, 1.1 Hz), 7.13 (m, 2H), 7.05 (d, 1H, J=16.3 Hz), 6.99 (d, 1H, J=1.0 Hz), 6.96 (d, 1H, J=16.3 Hz), 6.87 (d, 1H, J=8.4 Hz), 5.28 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.73 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.89, 156.05, 149.94, 149.62, 146.65, 138.88, 133.09, 130.34, 129.70, 128.71, 126.53, 125.88, 124.88, 121.24, 119.41, 118.82, 114.05, 111.75, 108.98, 108.12, 95.47, 56.17, 55.88, 55.74, 55.04; HRMS (FAB$^+$) m/z 451.1622 [M$^+$: calcd for $C_{25}H_{25}NO_7$, 451.1631]. Compound **38**: yellow oil, 439 mg, 0.972 mmol, 39%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, 1H, J=2.7 Hz), 7.27 (d, 1H, J=8.5 Hz), 7.14 (d, 1H, J=7.8 Hz), 7.13 (dd, 1H, J=8.5, 2.7 Hz), 7.09 (d, 1H, J=2.0 Hz), 6.96 (dd, 1H, J=7.7, 1.3 Hz), 6.94 (dd, 1H, J=8.5, 2.1 Hz), 6.80 (d, 1H, J=1.3 Hz), 6.78 (d, 1H, J=8.4 Hz), 6.54 (d, 1H, J=12.2 Hz), 6.50 (d, 1H, J=12.2 Hz), 5.07 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.49 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.93, 155.59, 150.12, 149.12, 145.98, 138.73, 133.11, 130.25, 129.90, 129.40, 128.71, 125.58, 124.99, 123.36, 121.88, 118.88, 117.22, 111.43, 110.94, 108.93, 95.47, 56.06, 55.84, 55.80, 54.89; HRMS (FAB$^+$) m/z 451.1643 [M$^+$: calcd for $C_{25}H_{25}NO_7$, 451.1631].

*4.1.25. 2-Amino-2′,4-dimethoxy-4′-[4-methoxy-3-(methoxymethoxy)phenethyl]biphenyl (**39**).* $Pd(OH)_2$ on carbon (10%, 50.0 mg) was added to a solution of **38** (459 mg, 1.02 mmol) in THF (10 ml) and methanol (20 ml), and the mixture was stirred for 1 day under hydrogen atmosphere. The reaction mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate 7:3) to give **39** (colorless oil, 364 mg, 0.860 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, 1H, J=7.6 Hz), 6.99 (d, 1H, J=8.4 Hz), 6.98 (s, 1H), 6.85 (dd, 1H, J=7.6, 1.4 Hz), 6.83 (d, 1H, J=1.0 Hz), 6.75 (d, 1H, J=1.1 Hz), 6.39 (dd, 1H, J=8.4, 2.5 Hz), 6.31 (d, 1H, J=2.4 Hz), 5.19 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.73–3.65 (br s, 2H), 3.51 (s, 3H), 2.95–2.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.94, 156.66, 148.06, 146.32, 145.53, 142.58, 134.47, 131.92, 131.79, 125.54, 122.12, 121.10, 117.84, 116.95, 111.82, 111.62, 103.99, 101.14, 95.57, 56.12, 55.96, 55.65, 55.05, 38.08, 37.14.

*4.1.26. 2-(4-Fluoro-3-nitrobenzamido)-2′,4-dimethoxy-4′-[4-methoxy-3-(methoxymethoxy)phenethyl]biphenyl (**40**).* A solution of 4-fluoro-3-nitrobenzoyl chloride (30.5 mg, 0.150 mmol, prepared from 4-fluoro-3-nitrobenzoic acid and oxalyl chloride) in methylene chloride (1.0 ml) was added dropwise to a solution of **39** (42.4 mg, 0.100 mmol) in THF (3.0 ml), and the mixture was stirred at 0 °C. After 1 h, the reaction mixture was poured into methanol at 0 °C, and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate 2:1 to 1:1) to give **40** (yellow oil, 56.0 mg, 0.095 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (br s, 1H), 8.24 (dd, 1H, J=6.8, 2.2 Hz), 8.12–8.08 (m, 1H), 7.80 (br s, 1H), 7.35 (dd, 1H, J=10.1, 8.8 Hz), 7.20 (d, 1H, J=8.5 Hz), 7.14 (d, 1H, J=8.0 Hz), 6.93–6.91 (m, 3H), 6.83–6.79 (m, 3H), 5.13 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.45 (s, 3H), 2.99–2.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.44, 159.54, 157.26 (d, J=270.9 Hz), 155.29, 148.05, 146.25, 143.91, 136.77 (d, J=7.6 Hz), 135.70, 135.02 (d, J=9.6 Hz), 134.09, 132.36, 131.97 (d, J=3.8 Hz), 131.76, 124.56, 124.06, 123.08, 122.37, 122.09, 119.19 (d, J=21.4 Hz), 116.91, 112.31, 111.77 (d, J=7.4 Hz), 107.53, 95.44, 56.40, 56.06, 55.92, 55.41, 37.92, 36.93; HRMS (FAB$^+$) m/z 591.2156 [(M+H)$^+$: calcd for $C_{32}H_{32}FN_2O_8$, 591.2143].

*4.1.27. 2-(4-Fluoro-3-nitrobenzamido)-2′,4-dimethoxy-4′-[3-hydroxy-4-methoxyphenethyl]biphenyl (**41**).* A solution of compound **40** (51.2 mg, 0.087 mmol) in THF (3.0 ml) and 4 M aqueous hydrochloric acid (1.0 ml) was stirred for 2 h at 50 °C. The reaction mixture was poured into ethyl acetate and water. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate 1:1) to give **41** (yellow solids, 41.3 mg, 0.076 mmol, 87%). Mp 191.0–191.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 8.35 (dd, 1H, J=7.0, 2.2 Hz), 8.06 (ddd, 1H, J=8.5, 4.0, 2.2 Hz), 7.79 (d, 1H, J=1.5 Hz), 7.57 (s, 1H), 7.50 (dd, 1H, J=10.7, 8.7 Hz), 7.17 (d, 1H, J=8.6 Hz), 7.15 (d, 1H, J=8.1 Hz), 7.00 (br s, 1H), 6.93 (dd, 1H, J=7.7, 1.2 Hz), 6.78 (dd, 1H, J=8.5, 2.6 Hz), 6.69 (d, 1H, J=2.0 Hz), 6.60 (dd, 1H, J=8.1, 2.1 Hz), 3.82 (s, 3H), 3.79 (s, 6H), 2.95–2.90 (m, 2H), 2.87–2.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.29, 160.41, 157.90 (d, J=277.5 Hz), 157.05, 147.79, 146.80, 144.88, 138.02 (d, J=7.7 Hz), 137.51, 135.58, 135.48 (d, J=10.4 Hz), 133.44 (d, J=3.8 Hz), 132.84, 132.45, 125.66 (d, J=20.8 Hz), 124.64, 122.39, 119.62 (d, J=21.7 Hz), 119.57, 116.36, 112.82, 112.05, 111.47, 109.34, 56.21 (2C), 55.56, 38.94, 37.99; HRMS (FAB$^+$) m/z 547.1867 [(M+H)$^+$: calcd for $C_{30}H_{28}FN_2O_7$, 547.1881].

*4.1.28. Macrolactam **42**.* Potassium carbonate (106 mg, 0.768 mmol) and 18-crown-6 (12.1 mg, 0.051 mmol) was added to a solution of **41** (140 mg, 0.256 mmol) in DMF (25 ml), and the mixture was stirred for 2 h at 45 °C. The reaction mixture was poured into ethyl acetate and water. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate 3:1 to 1:1) gave **42** (pale yellow solids, 99.8 mg, 0.190 mmol, 74%). Mp 176.5–177.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20–8.17 (m, 1H), 7.88–7.58 (m, 2H), 7.46–7.35 (m, 1H), 7.21–6.74 (m, 7H), 6.62–6.46 (m, 1H), 5.61–5.45 (m, 1H), 3.96–3.94 (m, 3H), 3.88 (s, 3H), 3.85–3.70 (m, 3H), 3.12–2.91 (m, 2H), 2.82–2.61 (m, 2H); HRMS (FAB$^+$) m/z 527.1832 [(M+H)$^+$: calcd for $C_{30}H_{27}N_2O_7$, 591.2143].

*4.1.29. Macrolactam **43**.* Palladium on carbon (10%, 20.0 mg) was added to a solution of **42** (62.5 mg, 0.012 mmol) in DMF (5.0 ml), and the mixture was stirred for 2 h under hydrogen atmosphere. The reaction mixture was filtered through Celite, and the filtrate was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate 3:2 to 2:3) to give **43** (colorless oil, 52.1 mg,

0.105 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.40 (m, 1H), 7.40–7.37 (m, 1H), 7.16–7.12 (m, 1H), 6.98–6.88 (m, 3H), 6.86–6.73 (m, 4H), 6.48–6.40 (m, 1H), 5.88–5.70 (m, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.90–3.85 (m, 1H), 3.10–2.85 (m, 2H), 2.78–2.54 (m, 2H).

4.1.30. Trimethoxymacrolactam ***44***. Aqueous hydrochloric acid (4 M, 1.0 ml) was added to a solution of **43** (46.7 mg, 0.094 mmol) in THF (4.0 ml) at 0 °C, and the mixture was stirred for 15 min at ambient temperature. A solution of $NaNO_2$ (19.5 mg, 0.283 mmol) in water (0.5 ml) was added to the mixture at 0 °C, and the mixture was stirred for 1 h at 0 °C. 50% H_3PO_2 (124 mg, 0.941 mmol) and Cu_2O (13.5 mg, 0.094 mmol) were added, and the mixture was stirred for 10 min at 0 °C, then 3 h at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 3:1) gave **44** (colorless oil, 30.6 mg, 0.064 mmol, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, 1H, *J*=8.2, 2.2 Hz), 7.53 (m, 1H), 7.48 (dd, 1H, *J*=8.4, 2.2 Hz), 7.45 (d, 1H, *J*=2.7 Hz), 7.14 (d, 1H, *J*=8.4 Hz), 7.02 (dd, 1H, *J*=8.4, 2.3 Hz), 6.98 (dd, 1H, *J*=8.4, 2.3 Hz), 6.94 (d, 1H, *J*=7.7 Hz), 6.90 (d, 1H, *J*=8.3 Hz), 6.84 (dd, 1H, *J*=8.3, 2.0 Hz), 6.78 (dd, 1H, *J*=8.4, 2.7 Hz), 6.76 (dd, 1H, *J*=7.7, 1.1 Hz), 6.50 (d, 1H, *J*=0.8 Hz), 5.63 (d, 1H, *J*=2.0 Hz), 3.94 (s, 3H), 3.87 (s, 3H), 3.71 (s, 3H), 3.03 (dd, 1H, *J*=14.3, 9.3 Hz), 2.97 (dd, 1H, *J*=14.0, 9.3 Hz), 2.77 (dd, 1H, *J*=14.0, 10.4 Hz), 2.66 (dd, 1H, *J*=14.3, 10.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.99, 159.75, 158.93, 155.50, 149.36, 147.90, 143.52, 137.00, 135.26, 133.62, 132.09, 130.41, 128.65, 126.82, 124.27, 123.97, 123.36, 122.63, 122.18, 121.45, 117.17, 112.46, 111.73, 111.45, 108.13, 56.21, 55.92, 55.48, 36.83, 34.69; HRMS (FAB^+) *m*/*z* 482.1958 [$(M+H)^+$: calcd for $C_{30}H_{28}NO_5$, 591.2143].

4.1.31. Macrolactam ***2***. Compound **2** was prepared from **44** (9.6 mg, 0.020 mmol) according to the synthetic procedure for **1** from **32**. Compound**2**: colorless oil, 7.8 mg, 0.018 mmol, 89%; ^{1}H NMR (500 MHz, THF-d_8) δ 8.40 (d, 1H, *J*=2.0 Hz), 8.26 (s, 2H), 7.69 (s, 1H), 7.61 (d, 1H, *J*=8.4 Hz), 7.49 (d, 1H, *J*=8.3 Hz), 7.37 (d, 1H, *J*=2.5 Hz), 7.02 (d, 2H, *J*=8.3 Hz), 6.91 (dd, 1H, *J*=8.4, 1.9 Hz), 6.82 (d, 1H, *J*=7.8 Hz), 6.80 (d, 1H, *J*=8.2 Hz), 6.76 (dd, 1H, *J*=8.2, 2.0 Hz), 6.62 (dd, 1H, *J*=7.7, 1.5 Hz), 6.57 (dd, 1H, *J*=8.2, 2.5 Hz), 6.38 (d, 1H, *J*=1.3 Hz), 5.68 (d, 1H, *J*=2.0 Hz), 2.95–2.87 (m, 2H), 2.68–2.58 (m, 2H); ^{13}C NMR (125 MHz, THF-d_8) δ 166.62, 160.74, 158.69, 154.30, 148.57, 147.17, 143.90, 138.52, 135.34, 134.60, 132.80, 131.21, 129.24, 128.12, 124.79, 123.73, 122.92, 122.74, 122.33, 121.28, 119.15, 117.52, 117.19, 112.16, 109.82, 37.80, 35.81; HRMS (FAB^+) *m*/*z* 440.1494 [$(M+H)^+$: calcd for $C_{27}H_{22}NO_5$, 440.1498].

4.1.32. N-Methylmacrolactam ***45***. Sodium hydride (60% in mineral oil, 2.0 mg, 0.050 mmol) was added to a solution of **44** (13.4 mg, 0.028 mmol) in DMF (2.0 ml), and the mixture was stirred for 10 min at 0 °C. Iodomethane (28.4 mg, 0.20 mmol) was added to the reaction vessel, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was poured into water at 0 °C, and diluted with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 2:1) to give **45** (colorless wax, 14.2 mg, 0.029 mmol, quant.); ^{1}H NMR (500 MHz, THF-d_8, 353 K) δ 7.48 (br s), 7.15 (d, 1H, *J*=8.6 Hz), 7.02 (d, 1H, *J*=2.7 Hz), 6.87 (dd, 1H, *J*=8.6, 2.7 Hz), 6.85 (d, 1H, *J*=8.0 Hz), 6.76 (d, 1H, *J*=8.2 Hz), 6.73–6.69 (d, 2H, *J*=8.9 Hz), 6.72 (dd, 1H, *J*=8.2, 2.0 Hz), 6.40 (s, 1H), 6.32 (dd, 1H, *J*=7.8, 1.4 Hz), 5.39 (d, 1H, *J*=2.1 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.64 (s, 3H), 3.50 (s, 3H), 2.89–2.75 (m, 2H), 2.74 (m, 2H); HRMS (FAB^+) *m*/*z* 496.2130 [$(M+H)^+$: calcd for $C_{31}H_{30}NO_5$, 496.2124].

4.1.33. N-Methylmacrolactam ***3***. Compound **3** was prepared from **45** (9.8 mg, 0.020 mmol) according to the synthetic procedure for **1** from **32**. Compound**3**: colorless solids, 6.5 mg, 0.014 mmol, 72%; mp 228.5–229.0 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.62 (br s, 1H), 7.87–7.75 (br m, 3H), 7.09 (br s, 1H), 7.01 (d, 1H, *J*=2.5 Hz), 6.87–6.78 (m, 2H), 6.84 (dd, 1H, *J*=8.9, 2.5 Hz) 6.81 (d, 1H, *J*=8.1 Hz), 6.70 (dd, 1H, *J*=8.1, 2.0 Hz), 6.38–6.33 (br m, 2H), 5.25 (br s, 1H), 3.56 (s, 3H), 2.76–2.50 (m, 4H); HRMS (FAB^+) *m*/*z* 454.1664 [$(M+H)^+$: calcd for $C_8H_{24}NO_5$, 454.1654].

Acknowledgements

The work described in this paper was partially supported by Grants-in-Aid for Scientific Research from The Ministry of Education, Science, Sports and Culture, Japan (Grant Nos 22790106 to T.H., 19201044 to H.K.). Authors are grateful to Prof. Yoshinori Asakawa and Prof. Toshihiro Hashimoto, Tokushima Bunri University, for a generous gift of the authentic sample of Riccardin C.

References and notes

1. (a) Zinsmeister, H. D.; Becker, H.; Eicher, T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 130–147; (b) Asakawa, Y. *Phytochemistry* **2001**, *56*, 297–312; (c) Asakawa, Y.; Toyota, M.; Hashimoto, T.; Tori, M.; Nagashima, F.; Harinantenaina, L. *Heterocycles* **2008**, *76*, 99–127.
2. Asakawa, Y.; Matsuda, R. *Phytochemistry* **1982**, *21*, 2143–2144.
3. Tamehiro, N.; Sato, Y.; Suzuki, T.; Hashimoto, T.; Asakawa, Y.; Yokoyama, S.; Kawanishi, T.; Ohno, Y.; Inoue, K.; Nagao, T.; Nishimaki-Mogami, T. *FEBS Lett.* **2005**, *579*, 5299–5304.
4. (a) Collins, J. L. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 692–702; (b) Bennett, D. J.; Carswell, E. L.; Cooke, A. J.; Edwards, A. S.; Nimz, O. *Curr. Med. Chem.* **2008**, *15*, 195–209; (c) Goodwin, B. J.; Zuercher, W. J.; Collins, J. L. *Curr. Top. Med. Chem.* **2008**, *8*, 781–791.
5. (a) Kodama, M.; Shiobara, Y.; Matsumura, K.; Sumitomo, H. *Tetrahedron Lett.* **1985**, *26*, 877–880; (b) Iyoda, M.; Sakaitani, M.; Otsuka, H.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 4777–4780; (c) Kodama, M.; Shiobara, Y.; Sumitomo, H.; Matsumura, K.; Tsukamoto, M.; Harada, C. *J. Org. Chem.* **1988**, *53*, 72–77; (d) Fukuyama, Y.; Yaso, H.; Nakamura, K.; Kodama, M. *Tetrahedron Lett.* **1999**, *40*, 105–108; (e) Fukuyama, Y.; Kodama, M.; Asakawa, Y. *J. Synth. Org. Chem.* **2000**, *58*, 654–665; (f) Esumi, T.; Wada, M.; Mizushima, E.; Sato, N.; Kodama, M.; Asakawa, Y.; Fukuyama, Y. *Tetrahedron Lett.* **2004**, *45*, 6941–6945; (g) Speicher, A.; Groh, M.; Hennrich, M.; Huynh, A.-M. *Eur. J. Org. Chem.* **2010**, 6760–6778.
6. (a) Gottsegen, Á; Nógrádi, M.; Vermes, B. *Tetrahedron Lett.* **1988**, *29*, 5039–5040; (b) Gottsegen, Á; Nógrádi, M.; Vermes, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 315–320.
7. Eicher, T.; Fey, S.; Puhl, W.; Büchel, E.; Speicher, A. *Eur. J. Org. Chem.* **1998**, 877–888.
8. Dodo, K.; Aoyama, A.; Noguchi-Yachide, T.; Makishima, M.; Miyachi, M.; Hashimoto, Y. *Bioorg. Med. Chem.* **2008**, *16*, 4272–7285.
9. Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 3899–3901.
10. Hioki, H.; Shima, N.; Kawaguchi, K.; Harada, K.; Kubo, M.; Esumi, T.; Nishimaki-Mogami, T.; Sawada, J.; Hashimoto, T.; Asakawa, Y.; Fukuyama, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 738–741.
11. (a) Zhu, J. *Synlett* **1997**, 133–144; (b) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045–5065; (c) Frlan, R.; Kikelj, D. *Synthesis* **2006**, *14*, 2271–2285.
12. Selected examples: (a) Beugelmans, R.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 5649–5652; (b) Gonzalez, G.-I.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 914–924; (c) Masuno, M.-N.; Pessah, I. N.; Olmstead, M. M.; Molinski, T. F. *J. Med. Chem.* **2006**, *49*, 4497–4511.
13. Boration: Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
14. Ozaki, S.; Adachi, M.; Sekiya, S.; Kamikawa, R. *J. Org. Chem.* **2003**, *68*, 4586–4589.
15. Arnusch, C. J.; Pieters, R. J. *Eur. J. Org. Chem.* **2003**, 3131–3138.
16. Boden, R. M. *Synthesis* **1975**, 784.
17. Heynekamp, J. J.; Weber, W. M.; Hunsaker, L. A.; Gonzales, A. M.; Orlando, R. A.; Deck, L. M.; Jagt, D. L. V. *J. Med. Chem.* **2006**, *49*, 7182–7189.
18. Xie, Z.; Yang, B.; Li, F.; Cheng, G.; Liu, L.; Yang, G.; Xu, H.; Ye, L.; Hanif, M.; Liu, S.; Ma, D.; Ma, Y. *J. Am. Chem. Soc.* **2005**, *127*, 14152–14153; (b) Hwang, J.-J.; Lin, R.-L.; Shieh, R.-L.; Jwo, J.-J. *J. Mol. Catal. A: Chem.* **1999**, *142*, 125–139; (c) Xie, Z.; Yang, B.; Liu, L.; Li, M.; Lin, D.; Ma, Y.; Cheng, G.; Liu, S. *J. Phys. Org. Chem.* **2005**, *18*, 962–973.
19. Jourdant, A.; Gonzalez-Zamora, E.; Zhu, J. *J. Org. Chem.* **2002**, *67*, 3163–3164.
20. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.
21. Gallou-Dagommer, I.; Gastaud, P.; RajanBabu, T. V. *Org. Lett.* **2001**, *3*, 2053–2056.