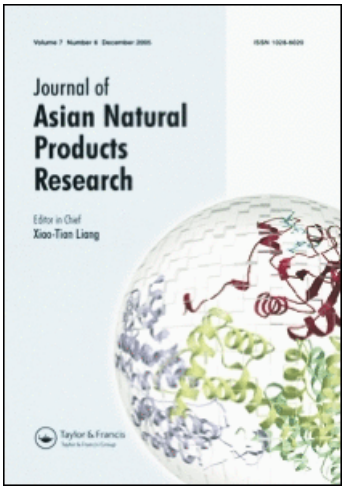


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# Total synthesis of adicardin

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# Total synthesis of adicardin

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The first synthesis of adicardin, a compound with anti-chronic renal failure activity isolated from *Hydrangea macrophylla*, has been described. The structures of the target compound and intermediates have been validated by MS, NMR, and identical with the natural product.

**Keywords:** adicardin; anti-chronic renal failure; synthesis; natural product



## 1. Introduction

Adicardin (Figure 1) with chemical name 7-(β-D-apiofuranosyl(1 → 6)-β-D-glucopyranosyl)umbelliferone, which was isolated from the roots and stems of *Gmelina arborea* (Verbenaceae) by Satyanarayana *et al.* [1], is the first coumarin glycoside containing apiose. In 1986, Asheervadam [2] obtained this compound from Rubiaceae and named adicardin. Adicardin was also isolated from the aerial parts of *Phlojodicarpus villosus* (Umbelliferae), and roots and stems of *Peucedanum praeruprography* Dunn [3]. Pharmacological research showed that adicardin has a favorable effect on chronic renal failure. Herein, we report the total synthesis of adicardin.

From the retrosynthesis, adicardin consists of two parts, apiose and skimming (7-β-D-glucopyranosyl-umbelliferone). Apiose, a branched aldopentose, was first isolated from parsley by Vongerichten [4] and existed in the form of apiin. Apiose has D- and L-configurations, and D-configuration is the common configuration in nature. Apiose exists in plants in the form of D-apiose, flavonoid glycosides, saponin, and phenylpropanoids, especially abundant in duckweeds. Also, apiose plays an important role in the physiological effect of natural products [5]. Recent pharmacological studies [6] showed that many glycosides containing apiose have favorable effects including anti-virus, anti-depression, anti-bairnsdale, anti-tumor, etc. There is no commercial apiose that can be used so far, so the synthesis of apiose is also included.

## 2. Results and discussion

Based on the related Refs [7–19], we design a reasonable route to synthesize adicardin. As shown in Scheme 1, adicardin (**1**) was synthesized from resorcin, glucose, and mannose in 20 steps. Cyclization of resorcin with malic acid affords **5**, which was acetylated to yield 7-β-D-(2,3,4,6-triacetyl) glucosylcoumarin (**6**). Deprotection of **6** with triethylamine

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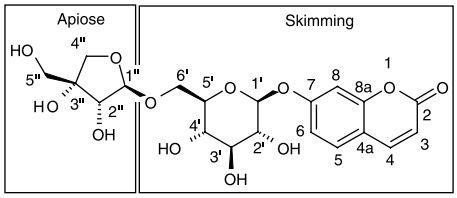



Figure 1. Chemical structure of adicardin.

in methanol afforded compound **7**. Protection of the hydroxymethyl with trityl chloride then gave **8**, which was acetylated with acetic anhydride to afford **9**, and after subsequent hydrogenolysis of the trityl group gave **10**. Coupling **10** with **19**, which was obtained from D-mannose through nine steps, afforded **20**. Finally, compound **1** was obtained by the deprotection of **20** with triethylamine. The total yield is 6.1% based on resorcin.

We tried another synthesis route that could be more simple and convenient as shown in Scheme 2. However, no matter which reagent was used, such as 30–80% TFA, $FeCl_3$–$SiO_2$, $BF_3$–$SiO_2$, or phenylethylene cation resin, etc., the propylidene cannot be eliminated effectively. Moreover, the raw material (compound **22**), the splitting product (compound **8**), and the target product (compound **1**) were difficult to separate. So we gave up this method.

Surprisingly, the specific rotation data of compound **1** were not consistent with those in the literatures [1,7,8]. After reviewing the references, we found that the data in the literatures are different from each other (Table 1). We presumed that the specific rotation data of natural products are effected by impurities, such as glucose compounds and so on. Our deduction can be strengthened by the identical NMR spectral data (Table 2), as well as the specific rotation data with those of the authentic sample provided by Professor D.M. Zhang. In conclusion, the target compound 7-(β-D-apiofuranosyl(1 → 6)-β-D-glucopyranosyl)umbelliferone (**1**) was prepared successfully by synthesis in an efficient manner (20 steps, 6.1% yield). This provides not only a new example of synthesis route of adicardin, but also new specific rotation data that are more accurate.

## 3. Experimental

### *3.1 General experimental procedures*

Melting points were obtained on an RTY-33 temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 2400 MC Autopol polarimeter. $^1$H NMR spectra were recorded on a Varian Mercury-300 or Mercury-400 NMR spectrometer, and mass spectra on an Autospec-Ultima ETOF. TLC was carried out on silica gel layers and detected by UV at 254 nm (provided by Yan Tai Chemical Industry Research Institute, Yantai, China).

### *3.2 1,2,3,4,6-Pentaacetylglucose (2)*

1,2,3,4,6-Pentaacetylglucose (**2**) was prepared via a method similar to the literature [9] with a yield of 95.3%.

### *3.3 2,3,4,6-Tetraacetylglucose (3)*

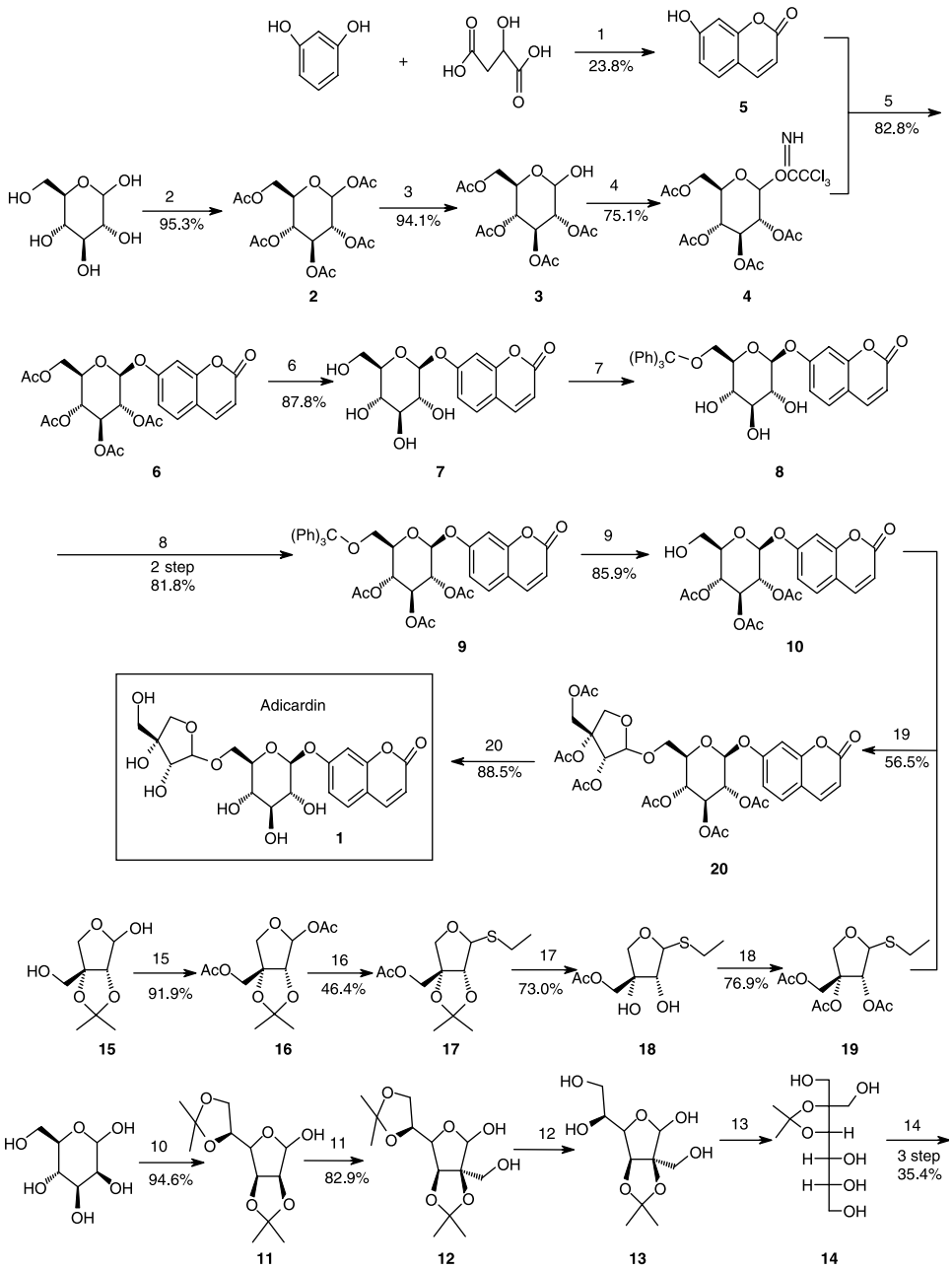
2,3,4,6-Tetraacetylglucose (**3**) was prepared via a method similar to the literature [10] with a yield of 94.1%.

### *3.4 2,3,4,6-Tetraacetylglucose trichloroacetimidate (4)*

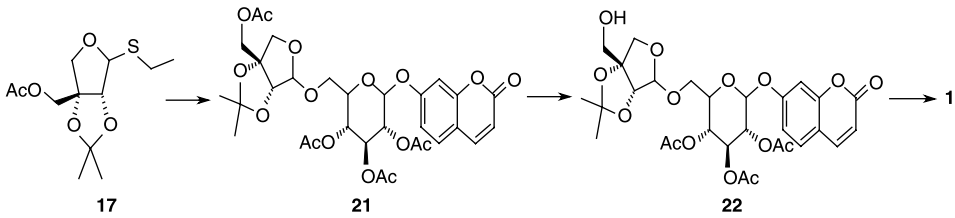
2,3,4,6-Tetraacetylglucose trichloroacetimidate (**4**) was prepared via a method similar to the literature [11] with a yield of 75.1%.

### *3.5 7-Hydroxycoumarin (5)*

According to the literature [12], 7-hydroxycoumarin (**5**) was synthesized with a yield of 23.8%, mp: 234–235°C (225°C [12]).




Scheme 1. The synthesis route of adicardin. Reagents and conditions. (1) Conc. $H_2SO_4$; (2) $Ac_2O$, pyridine; (3) $H_2NNH_2{\cdot}AcOH$, DMF; (4) $NCCl_3$, DBU–$CH_2Cl_2$; (5) $BF_3{\cdot}Et_2O$–$CH_2Cl_2$; (6) TEA, MeOH; (7) $(Ph)_3CCl$, pyridine; (8) $Ac_2O$, pyridine; (9) $FeCl_3$, MeOH–$CH_2Cl_2$; (10) $CH_3COCH_3$, conc. $H_2SO_4$; (11) 37% HCHO, $K_2CO_3$–MeOH; (12) conc. $H_2SO_4$, MeOH–$H_2O$; (13) $NaBH_4$, $H_2O$; (14) $NaIO_4$, $H_2O$; (15) $Ac_2O$, DMAP–pyridine; (16) EtSH, $BF_3{\cdot}Et_2O$–$CH_2Cl_2$; (17) 70% $CF_3COOH$; (18) $Ac_2O$, DMAP–pyridine; (19) NIS, TMSOTf–$CH_2Cl_2$; (20) TEA, MeOH.




Scheme 2. Another synthesis route of adicardin.

### 3.6 7-β-D-(2,3,4,6-Triacetyl) glucosylcoumarin (6)

7-β-D-(2,3,4,6-Triacetyl) glucosylcoumarin (**6**) was prepared via a method similar to the literature [13] with a yield of 82.8%, mp: 177–179°C (183–184°C [13]).

### 3.7 7-β-D-Glucosylcoumarin (7)

7-β-D-Glucosylcoumarin (**7**) was prepared via a method similar to the literature [14] with a yield of 87.8%.

### 3.8 7-β-D-(6-Trityl) glucosylcoumarin (8)

According to the literature [14], compound **7** (0.5 g, 1.54 mmol) and trityl chloride (0.475 g, 1.7 mmol) were dissolved in dry pyridine (5 ml). The mixture was stirred for 5 h at 80°C to give **8**.

### 3.9 7-β-D-(2,3,4-Triacetyl-6-trityl) glucosylcoumarin (9)

Compound **8** was added to dry pyridine (5 ml). A mixed solution of acetic anhydride and pyridine (1:1, 8 ml) was added dropwise to maintain the temperature below 0°C; the mixture was stirred for one night at room temperature, diluted with $CH_2Cl_2$ (200 ml), and then washed with hydrochloric acid (2 mol/l, 150 ml × 3) and brine (150 ml × 2). The organic layer was dried with anhydrous sodium sulfate and the mixture was concentrated and then separated on a silica gel column with petroleum ether–ethyl acetate (3:1) to give a white solid (**9**) (0.88 g, 81.8%).

### 3.10 7-β-D-(2,3,4-Triacetyl) glucosylcoumarin (10)

Compound **9** (5.56 g, 8.03 mmol) and iron trichloride (2.7 g, 16.1 mmol) were added to the mixed solution of $CH_2Cl_2$ (40 ml) and methanol (20 ml). The mixture was stirred for 3 days at room temperature, diluted with $CH_2Cl_2$ (200 ml), and then washed with brine (200 ml × 5). The organic layer was dried with anhydrous sodium sulfate and the mixture was concentrated and then separated on a silica gel column with $CH_2Cl_2$–methanol (20:1) to give a white solid (**10**) (3.1 g, 85.9%). mp: 168–169°C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$/ppm: 7.65 (1H, d, $J = 9.6$ Hz); 7.41 (1H, d, $J = 8.4$ Hz); 6.92–6.90 (2H, m); 6.32 (1H, d, $J = 9.6$ Hz); 5.37 (1H, t, $J = 9.2$ Hz); 5.28 (1H, t, $J = 9.2$ Hz); 5.26–5.14 (2H, m); 3.82 (1H, d, $J =$ 12.4 Hz); 3.73–3.64 (2H, m); 2.21 (1H, d, $J = 5.6$ Hz, $D_2O$, exchangeable); 2.09 (3H, s); 2.06 (3H, s); 2.05 (3H, s). FAB-MS *m/z*: 451 $[M+H]^+$.

### 3.11 2,3,5,6-Dipropylidene-D-mannofuranose (11)

According to the literature [15], 2,3,5,6-dipropylidene-D-mannofuranose (**11**) was synthesized with a yield of 94.6%.

### 3.12 2-Hydroxymethyl-2,3,5,6-dipropylidene-D-mannofuranose (12)

2-Hydroxymethyl-2,3,5,6-dipropylidene-D-mannofuranose (**12**) was prepared via a method similar to the literature [16] with a yield of 82.9%, mp: 103–104°C.

Table 1. The reference data of specific rotation and melting point of adicardin.

| | Sample prepared by synthesis | Authentic sample provided by Professor D.M. Zhang | Satyanarayana *et al.* [1] | Gantimur *et al.* [8] | Kithsiri *et al.* [7] |
|---|---|---|---|---|---|
| Specific rotation | $[\alpha]_D^{25} - 135$ ($c = 0.59$, $H_2O$–$CH_3OH$ = 1:1) | $[\alpha]_D^{25} - 133$ ($c = 0.30$, $H_2O$–$CH_3OH$ = 1:1) | $[\alpha]_D^{25} - 38$ | $[\alpha]_D^{25} + 169$ ($c = 0.59$, $H_2O$–$CH_3OH$ = 1:1) | $[\alpha]_D^{25} - 127$ ($c = 1.0$, pyridine) |
| mp | 201–202 (methanol) | 196–197 (methanol) | 141–142 (methanol) | 204–205 (methanol) | 138–140 (methanol–chloroform = 3:7) |

### *3.13 2-Hydroxymethyl-2,3-propylidene-D-mannofuranose (13)*

According to the literature [17], 2-hydroxymethyl-2,3-propylidene-D-mannofuranose (**13**) was synthesized.

### *3.14 2-Hydroxymethyl-2,3-propylidene-D-mannitol (14)*

2-Hydroxymethyl-2,3-propylidene-D-mannitol (**14**) was prepared via a method similar to the literature [17].

### *3.15 2,3-Propylidene-β-D-apiose (15)*

2,3-Propylidene-β-D-apiose (**15**) was prepared via a method similar to the literature [18] with a yield of 35.4%.

### *3.16 1,5-Diacetyl-2,3-propylidene-β-D-apiose (16)*

1,5-Diacetyl-2,3-propylidene-β-D-apiose (**16**) was prepared via a method similar to the literature [19] with a yield of 91.9%.

### *3.17 1-Ethylthio-2,3-propylidene-5-acetyl-β-D-apiose (17)*

Compound **16** was dissolved in dry dichloromethane (40 ml) and the mixture was stirred for 30 min under ice cooling. Then, ethanethiol (1.47 ml, 19.6 mmol) was added in this solution. After stirring for 30 min, the mixed solution of boron trichloride ether solution (2.1 ml) and dichloromethane (8 ml) was added. The mixture was stirred for one night, neutralized with sodium bicarbonate under ice cooling, and washed with brine (50 ml × 3). The organic layer was dried with anhydrous sodium sulfate and the mixture was concentrated and then separated on a silica gel column with petroleum ether–ethyl acetate (20:1) to give a yellow oil (**17**) (1.4 g, 46.4%). ESI-MS *m/z*: 275.3 $[M+K]^+$, 259.4 $[M+Na]^+$.

Table 2. $^{1}H$ and $^{13}C$ NMR spectral data of adicardin (400 MHz for $^{1}H$ and 100 MHz for $^{13}C$ NMR in DMSO-$d_6$).

| | Sample prepared by synthesis | Gantimur *et al.* [8] | Sample prepared by synthesis | Gantimur *et al.* [8] | Satyanarayana *et al.* [1] |
|---|---|---|---|---|---|
| Atom | $\delta_H$ ($J$ in Hz) | | $\delta_C$ | | |
| 2 | | | 160.2 | 160.9 | 160.4 |
| 3 | 6.32 d (9.2) | 6.32 d (10) | 113.2 | 114.0 | 113.6 |
| 4 | 7.99 d (8.2) | 7.99 d (10) | 144.2 | 144.8 | 144.0 |
| 4a | | | 113.3 | 114.1 | 113.6 |
| 5 | 7.64 d (8.2) | 7.64 d (9) | 129.5 | 130.2 | 129.7 |
| 6 | 7.02–7.00 m | 7.02–7.00 m | 113.4 | 114.2 | 113.6 |
| 7 | | | 160.1 | 160.9 | 160.4 |
| 8 | 7.02–7.00 m | 7.02–7.00 m | 103.3 | 104.2 | 103.5 |
| 8a | | | 155.0 | 155.7 | 155.2 |
| 1′ | 4.98 d (7.2) | 4.98 d (7) | 99.9 | 101.1 | 100.2 |
| 2′ | 3.73 dd (6.4, 3.2) | | 73.4 | 73.9 | 73.6 |
| 3′ | 3.59–3.57 m | | 73.1 | 76.8 | 73.3 |
| 4′ | 3.59–3.57 m | | 69.8 | 70.7 | 70.1 |
| 5′ | 3.44 dd (11.2, 3.2) | | 76.4 | 77.2 | 76.3 |
| 6′ | 3.16–3.11 m | | 67.6 | 68.3 | 67.9 |
| 1″ | 4.79 d (3.6) | 4.79 d (3) | 109.3 | 110.1 | 109.4 |
| 2″ | 3.88 d (9.2) | | 75.9 | 76.4 | 76.3 |
| 3″ | | | 78.7 | 79.4 | 79.0 |
| 4″ (2H) | 3.30–3.25 m | | 75.5 | 74.2 | 73.6 |
| 5″ (2H) | 3.39–3.31 m | | 63.2 | 64.3 | 63.5 |
| —OH | 5.40 d (4.8) | | | | |
| —OH | 5.17 t (6.4) | | | | |
| —OH | 5.17 t (6.4) | | | | |
| —OH | 5.01 d (7.2) | | | | |
| —OH | 4.71 t (6.0) | | | | |
| —OH | 4.46 s | | | | |



### 3.18 1-Ethylthio-5-acetyl-β-D-apiose (18)

Compound **17** (1.86 g, 6.73 mmol) was added to 70% trifluoroacetic acid (20 ml). The mixture was stirred for one night at room temperature, diluted with water (50 ml) and ethyl acetate (50 ml) under ice cooling, and neutralized with sodium bicarbonate. The liquid layer was extracted with ethyl acetate (50 ml × 3). The organic layer was dried with anhydrous sodium sulfate and the mixture was concentrated and then separated on a silica gel column with petroleum ether–ethyl acetate (2:1) to give a yellow oil (**18**) (1.16 g, 73.0%). ESI-MS *m/z*: 343.4 $[M+Na]^+$.

### 3.19 1-Ethylthio-2,3,5-triacetyl-β-D-apiose (19)

Compound **18** (0.1 g, 0.42 mmol) was added to dry pyridine (3 ml). The mixture was stirred under ice cooling for 30 min. Acetic anhydride (1 ml) and 4-*N*,*N*-dimethylpyridine (50 ml) were added dropwise to this solution. After being stirred for one night at room temperature, the mixture was diluted with water (20 ml) and dichloromethane (20 ml) under ice cooling, and neutralized with hydrochloric acid (2 N). The liquid layer was extracted with dichloromethane (20 ml × 3). The extract was washed with hydrochloric acid (2 N, 50 ml × 3) and brine (50 ml × 2). The organic layer was dried

with anhydrous sodium sulfate and evaporated under reduced pressure to give a yellow oil (**19**) (0.1 g, 76.9%).

### *3.20 7-(β-D-2,3,5-Triacetylapiofuranosyl(1 → 6)-β-D-2,3,4-triacetylglucopyranosyl) umbelliferone (20)*

Compound **19** (0.1 g, 0.31 mmol), compound **9** (0.1 g, 0.22 mmol), and adequate molecular sieves were added in dry dichloromethane (20 ml). After being stirred at −20°C for 15 min, *N*-iodosuccinimide (60 mg, 0.26 mmol) was added to this solution. After 30 min, trimethylsilyl trifluoromethanesulfonate (2 drops) was added. The mixture was stirred for 5 min, concentrated, and then separated on a silica gel column with petroleum ether–ethyl acetate (3:1) to give a white solid (**20**) (0.1 g, 56.5%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$/ppm: 7.65 (1H, d, $J = 9.2$ Hz), 7.43 (1H, d, $J = 8.8$ Hz), 6.94 (1H, s), 6.92 (1H, d, $J = 2.0$ Hz), 6.31 (1H, d, $J = 9.6$ Hz), 5.33 (1H, brs), 5.30 (1H, d, $J = 6.0$ Hz), 5.26 (1H, t, $J = 9.2$ Hz), 5.17 (1H, d, $J = 7.2$ Hz), 5.07 (1H, t, $J = 9.2$ Hz), 5.05–4.78 (1H, m), 4.76 (1H, d, $J = 12.4$ Hz), 4.55 (1H, d, $J = 12.4$ Hz), 4.20 (1H, d, $J = 10.8$ Hz), 4.12 (1H, d, $J = 10.8$ Hz), 3.86 (1H, dd, $J = 6.4, 1.6$ Hz), 3.78 (1H, dd, $J = 11.6, 2.0$ Hz), 3.61 (1H, dd, $J = 11.6, 6.4$ Hz), 2.11 (3H, s), 2.07 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 2.01 (6H, s). ESI-MS *m/z*: 747.3 $[M+K]^+$, 731.3 $[M+Na]^+$, 709.3 $[M+H]^+$.

### *3.21 7-(β-D-Apiofuranosyl(1 → 6)-β-D-glucopyranosyl)umbelliferone (1)*

Compound **20** (100 mg, 0.14 mmol) and triethylamine (3 drops) were added to methanol (4.0 ml). After refluxing for 6 h, the solvent was evaporated under reduced pressure, and the residue was recrystallized from methanol to give a white solid (**1**) (57 mg, 88.5%). FAB-MS *m/z*: 495.1 $[M+K]^+$, 479.3 $[M+Na]^+$, 457.3 $[M+H]^+$.

## Acknowledgements

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## Note

1. Equal contributions to this work.

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