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Article

Mild and Selective Method of Bromination of Flavonoids

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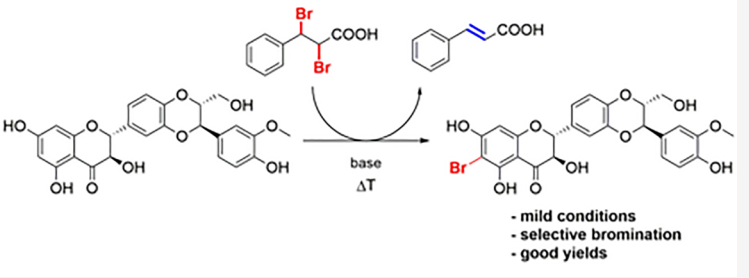

ABSTRACT: A new method was developed for the mild and selective bromination of simple aromatic compounds and flavonoids in good yields using α,β-dibromohydrocinnamic acid in the presence of a base. This procedure enables selective mono- or dibromination of compounds highly sensitive to oxidative or radical attack. New brominated derivatives of silymarin flavonolignans and related flavonoids were prepared. These brominated derivatives can be used as valuable synthetic intermediates in further synthesis.

Halogens are useful functional groups that form an important part of the repertoire of core organic chemistry. Aryl bromides occur widely in nature, most commonly in marine organisms; in chemistry, they are indispensable synthetic intermediates.[1] Bromination is a standard method for preparing reactive intermediates for consecutive use in organic synthesis (palladium-catalyzed cross-coupling reactions, Buchwald−Hartwig reaction, among others). We aimed to prepare selectively brominated flavonolignans, a group of compounds that has not been described so far.

Flavonoids [e.g., taxifolin (**1**), quercetin (**2**), myricetin (**3**)] form a vast group of phenolic secondary metabolites found in most plants, also in fungi, and they commonly are part of the human diet.[2] Flavonoids typically have low toxicity for humans; their beneficiary biological effects such as antioxidative, anti-inflammatory, antimutagenic, and cytotoxic properties are well known.[3] Flavonolignans are a relatively small subclass of natural flavonoids, where the flavonoid part of the molecule is fused with a monolignol moiety.[2] A crude extract from the fruits of *Silybum marianum* (silymarin), which is widely used in nutraceutical preparations and herbal drugs, contains silybin A (**4a**), silybin B (**4b**), dehydrosilybin (**5**), silychristin A (**6**), dehydrosilychristin (**7**), isosilybin, silydianin, and other minor compounds.[4] Flavonolignans and their derivatives generally have low or negligible toxicity and interesting biological activities such as hepatoprotective and anti-inflammatory effects. Some flavonolignans were recently described to inhibit transporters associated with multidrug resistance.[5]

Commonly used bromination techniques for aromatic compounds make use of elementary bromine, HBr, *N*-bromosuccinimide (NBS), and also other brominated compounds and salts, which can be a source of electrophilic bromine (Br^+).[6] The use of elementary bromine is the predominant approach for producing brominated derivatives, but it suffers from various limitations; most importantly it is a hazardous, toxic, and corrosive reagent. Moreover, elementary bromine is a strong oxidizing agent with a high first ionization energy; therefore it is unsuitable for reaction with compounds sensitive to oxidation. Therefore, brominations with Br_2 and HBr are considered harsh and often lead to substrate decomposition. Nagimova et al. reported the use of Br_2 (1.2 equiv) for quercetin bromination to produce 6-bromoquercetin. Dibromination at C-6 and C-8 proceeded with 2.4 equiv of Br_2 in HOAc. The use of a higher bromine concentration yielded a mixture of brominated products containing several bromo substituents.[7] Bromination with HBr/DMSO was reported by Song et al. This oxidative halogenation is useful for the late-stage bromination of natural products and has significant industrial potential; however, it was not demonstrated for flavonoids.[8] NBS is a widely used and easy to handle bromination reagent. It is suitable as a source of bromine for

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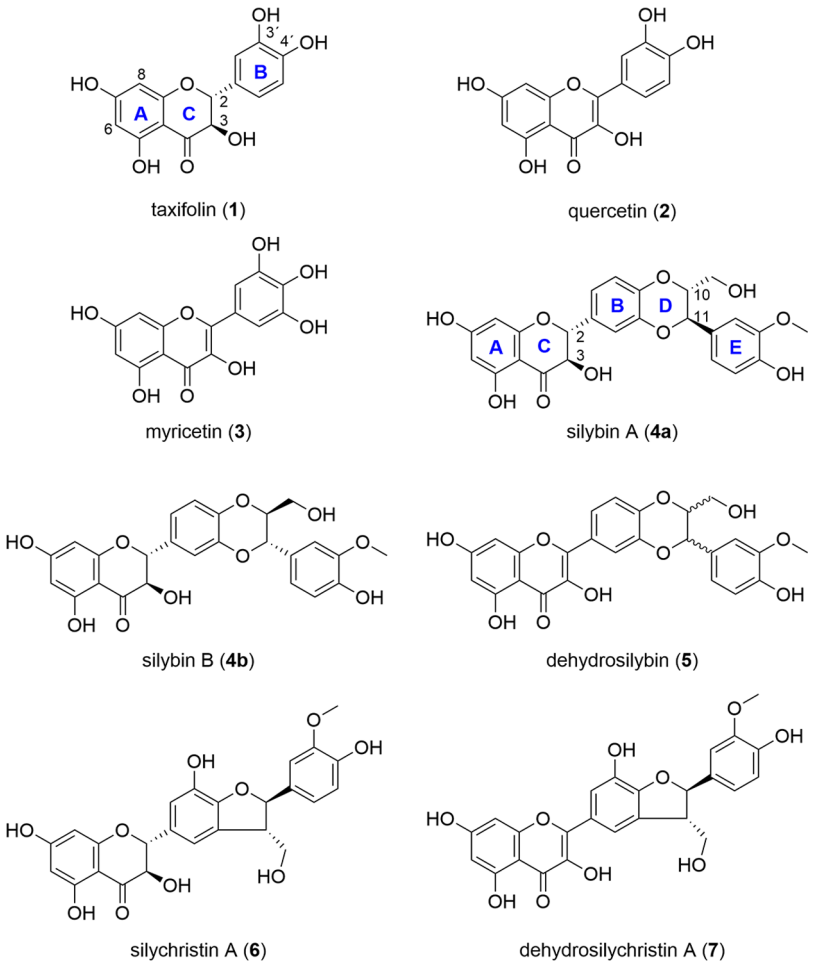
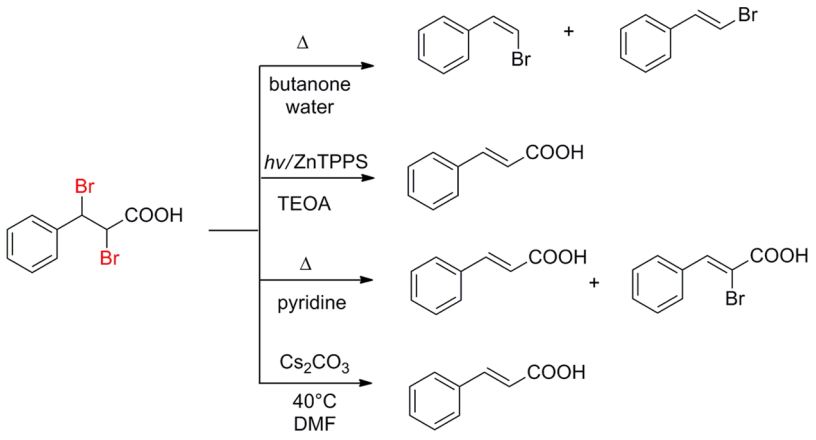
Chart 1



Scheme 1. Decomposition of α,β-Dibromohydrocinnamic acid[23−25]



radical substitution on aliphatic compounds[9] and electrophilic substitution on an aromatic moiety.[10,11]

The bromination of quercetin with NBS yields a mixture of 6-bromo, 8-bromo, and 6,8-dibromoquercetin.[12,13] Pan et al. published a method for the regioselective bromination of quercetin at C-6 or C-8 with NBS. Different regioselectivity was achieved, depending on the protection of the HO-5 and HO-7 group (methyl, ethyl, isopropyl) at low temperatures (−40 °C).[14] 8-Bromotaxifolin can be prepared from 6,8-dibromotaxifolin by a partial debromination with $NaHCO_3$ and Na_2SO_3 in aqueous MeOH.[15] Brominated derivatives of flavonoids, namely flavanones, flavones, and flavan-3-ols, were prepared with a mixture of NaBr and H_2O_2 in HOAc. The regioselectivity of bromination was controlled by the methylation of hydroxy groups on the A-ring.[16] The use of oxone and KBr was recently described for the bromination of flavones at C-3 of the C-ring.[17] An example of an organic bromo derivative employed for regioselective bromination is the application of dibromoisocyanuric acid in H_2SO_4 for aromatic compounds with strongly deactivating substitu-

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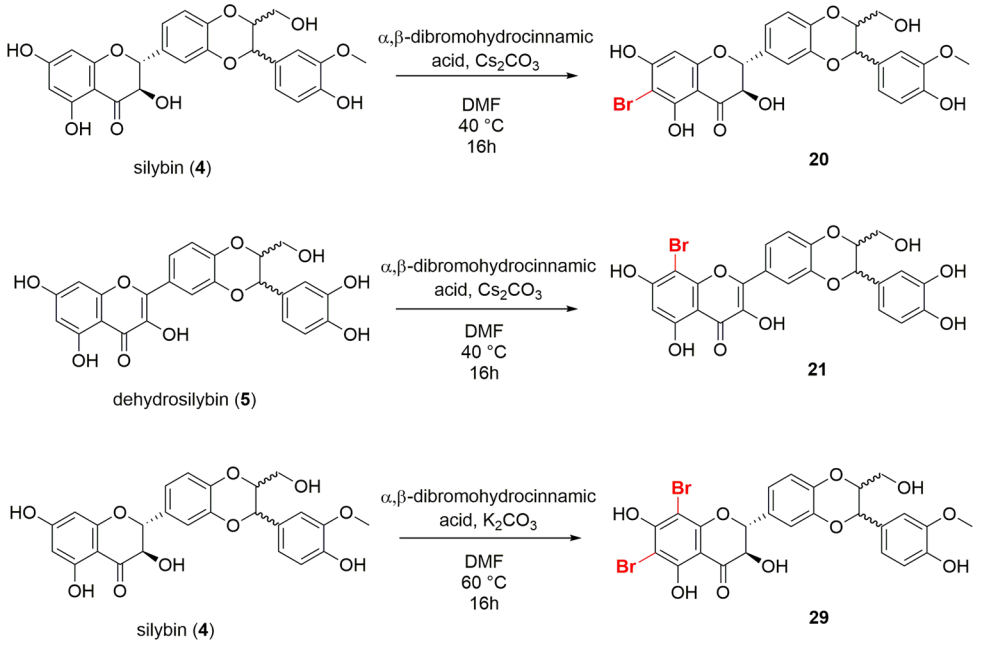
Scheme 2. Bromination of Silybin (4, Natural Diastereomeric Mixture) and Dehydrosilybin (5, Racemic) with α,β-Dibromohydrocinnamic Acid



ents.[18,19] Reaction conditions are harsh and not suitable for more complex and functionalized compounds. Tetrabutylammonium tribromide [TBATB; $Bu_4N^+(Br_3)^-$] is a milder bromination agent used for the bromination of aromatic compounds and labile substrates such as imidazole and ketones.[20] The bromination of aliphatic and aromatic compounds with tetrabromocardanol was reported by Attanasi et al.[21] Owing to the above-mentioned shortcomings, the development of a mild and regioselective bromination method for aromatic compounds is still a prime objective.

We have discovered that α,β-dibromohydrocinnamic can be used for the bromination of some aromatic compounds. α,β-Dibromohydrocinnamic (2,3-dibromo-3-phenylpropanoic) acid is commercially available, or it can be readily prepared by the bromination of cinnamic acid.[22] The dibromo acid can undergo decarboxylative elimination, elimination of HBr, or elimination of bromine in the presence of a base. The main product of decarboxylative elimination is *cis*- (*Z*) or *trans*- (*E*) bromostyrene, depending on the polarity of the solvent used.[23] The debromination of α,β-dibromohydrocinnamic acid was studied as photodebromination with zinc tetrasodium tetrakis-(sulfonatophenyl)porphyrin (ZnTPPS) in the presence of triethanolamine (TEOA).[24] Pffeifer described the formation of cinnamic acid as a product of bromine elimination from α,β-dibromohydrocinnamic acid in pyridine as a solvent. The second isolated product was α-bromocinnamic acid, the product of HBr elimination[25] (Scheme 1). We report here the use of α,β-dibromohydrocinnamic acid for the bromination of flavonoids and some other aromatic compounds.

RESULTS AND DISCUSSION

The reaction we developed employs bromine slowly released from α,β-dibromohydrocinnamic acid, which can be used for the bromination of aromatic compounds. The bromination reaction was tested with a maximum of 0.5 equiv of base (Cs_2CO_3, K_2CO_3, or pyridine). With the amount of base exceeding 0.5 equiv, the elimination of bromine is accompanied by the elimination of HBr. The controlled and slow release of bromine at lower temperatures can brominate compounds sensitive to oxidation with high regioselectivity. This method was used for the preparation of brominated derivatives of flavonolignans, which is an especially challenging task for several reasons. The use of elementary bromine is not feasible due to the harsh reaction conditions and their inherent sensitivity to oxidation. The regioselective method published by Pan et al.[14] for the bromination of alkyl ethers of quercetin cannot be used for flavonolignans. It is impossible to protect silybin with the use of isopropyl iodide due to differences in reactivity of −OH groups toward the etherification reaction and partial oxidation of silybin to 2,3-dehydrosilybin under harsh alkaline conditions. Additionally, deprotection using BBr_3 may lead to the isomerization of flavonolignans.[26] The use of 1 equiv of NBS with unprotected silybin yields an inseparable mixture of starting material, 6-bromo, 8-bromo, and 6,8-dibromosilybin in a 1:1:1 ratio (HPLC). The bromination of unprotected taxifolin using NBS leads to partial oxidation to quercetin. Owing to these challenges, the attempts to prepare these compounds via the previously mentioned conventional methods failed.

In contrast, the use of α,β-dibromohydrocinnamic acid in the presence of a base (0.5 equiv) at 40 °C yields selective monobromination at C-6 of taxifolin (**1**), silybin (**4**), and silychristin A (**6**), devoid of the 2,3-double bond. Under the same conditions, compounds with a 2,3-double bond [quercetin (**2**), myricetin (**3**), dehydrosilybin (**5**), dehydrosilychristin (**7**)] afforded C-8 derivatives (Scheme 2). The high regioselectivity of the bromination of flavonolignans with this method is achieved via low reaction temperature and by the strong directing effects of HO-5 and HO-7.

6,8-Disubstitution with bromine can be achieved by using a different base and higher temperature (Scheme 2). The reaction proceeds faster in the presence of K_2CO_3 (compared with Cs_2CO_3), and the elimination of bromine is favored at higher temperatures. At temperatures over 60 °C di- and

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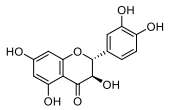
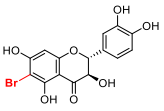
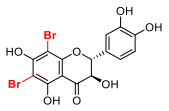
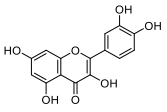
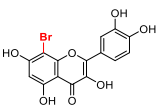
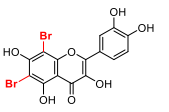
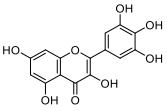
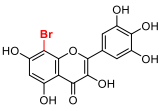
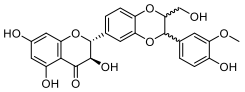
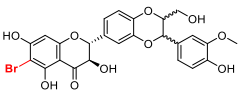
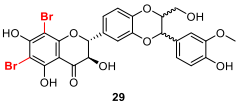
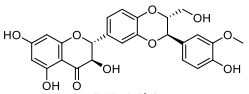
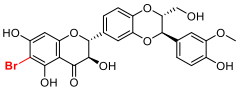
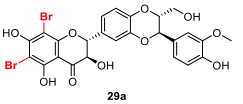
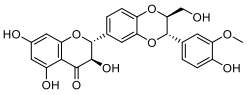
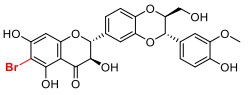
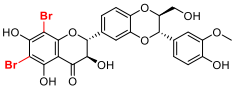
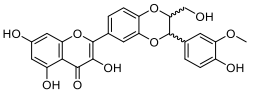
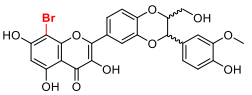
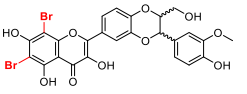
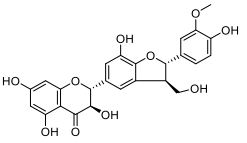
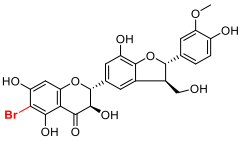
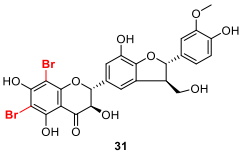
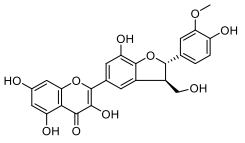
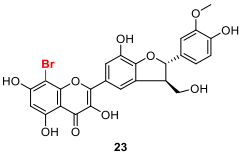
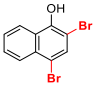
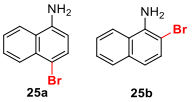
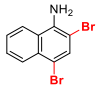
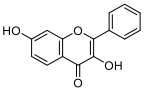
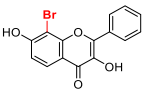
Table 1. Structures of Prepared Derivatives and Isolated Yields

Starting material	Method	Product of monobromination	Isolated yield [%]	Method	Product of dibromination	Isolated yield [%]
 taxifolin (**1**)	A	 **17**	40	B	 **27**	46
 quercetin (**2**)	A	 **18**	25	B	 **28**	50
 myricetin (**3**)	A	 **19**	49			
 silybin AB (**4**)	A	 **20**	36	B	 **29**	47
 silybin A (**4a**)	A	 **20a**	30	B	 **29a**	42
 silybin B (**4b**)	A	 **20b**	35	B	 **29b**	42
 dehydrosilybin AB (**5**)	A	 **21**	30		 **30**	30
 silychristin A (**6**)	A	 **22**	55	B	 **31**	43
 dehydrosilychristin A (**7**)	A	 **23**	20			
 1-naphthol (**8**)	A	 **24**	46	B	 **32**	41
 1- naphtylamine (**9**)	A	 **25a** **25b**	44	B	 **33**	44
 3,7-dihydroxyflavone (**10**)	A	 **26**	40			

[A] α,β-Dibromohydrocinnamic acid, Cs_2CO_3, DMF, 40 °C, 16 h. [B] α,β-Dibromohydrocinnamic acid, K_2CO_3, DMF, 60 °C, 16 h.

tribromination occur; in the case of flavonolignans temperatures over 90 °C lead to oxidative desaturation of the C-2−C-3 bond and formation of a complex mixture of brominated products.

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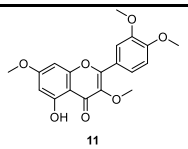
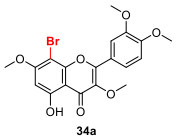
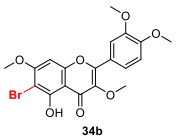
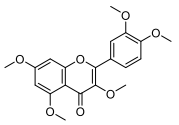
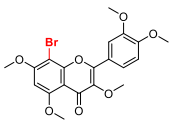
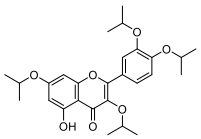
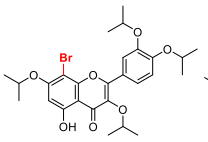
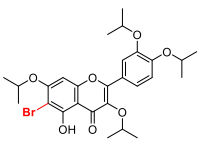
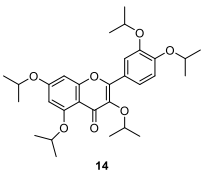
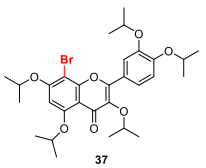
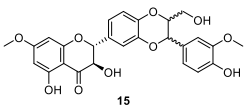
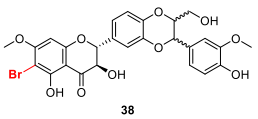
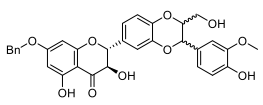
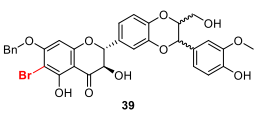
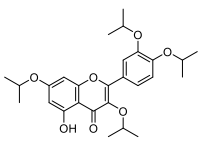
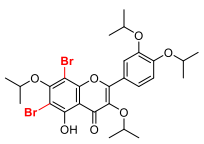
Table 2. Structure of Derivatives with Alkylated Hydroxy Groups and Isolated Yields

Starting material	Method	Product of monobromination	Isolated yield [%]
 11	A	 34a  34b	43
 12	A	 35	41
 13	A	 36a  36b	25 32
 14	A	 37	40
 15	A	 38	30*
 16	A	 39	44*
 13	B	 40	46

[A]α,β-Dibromohydrocinnamic acid, Cs_2CO_3, DMF, 40 °C, 16 h. [B]α,β-Dibromohydrocinnamic acid, K_2CO_3, DMF, 60 °C, 16 h. *Product was isolated as a mixture containing 20% of 8-bromo derivative.

The bromination of luteolin (3′,4′,5,7-tetrahydroxyflavone) yielded an inseparable mixture of a dibrominated (93%) and a monobrominated derivative (7%). The ratio of components in the mixture was determined *via* HPLC/MS analysis.

The method was also used for monobromination of 3,7-dihydroxyflavone (**10**), which lacks the HO-5 group, and this reaction yields only the C-8 monobrominated product (**26**). Bromination under conditions used for dibromination of 3,7-dihydroxyflavone yields only the C-8 monobrominated product.

When the HO-7 group is modified [3,3′,4′,7-tetra-*O*-methylquercetin (**11**), 3,3′,4′,7-tetra-*O*-isopropylquercetin (**13**), 7-*O*-methylsilybin AB (**15**), 7-*O*-benzylsilybin AB (**16**)], the reaction lost the regioselectivity, and monobromination yields a mixture of 6- and 8-brominated products. This reaction course is probably caused by different directing and/or steric effects of ethereal compared with hydroxy groups.

When both HO-5 and HO-7 groups are protected [3,3′,4′,5,7-penta-*O*-methylquercetin (**12**), 3,3′,4′,5,7-penta-*O*-isopropylquercetin (**14**)], the reactions under both mono- and dibromination conditions lead to single substitution at C-8. 3,3′,4′,7-Tetra-*O*-isopropylquercetin (**13**) lacking the protection of the HO-5 group afforded the 6,8-dibromo derivative (**40**) in 46% yield.

The method can also be used for the bromination of simple aromatic compounds. 1-Naphthol (**8**) in the presence of α,β-dibromohydrocinnamic acid and Cs_2CO_3 at 40 °C yields 2-bromo-1-naphthol (**24**). In the case of 1-naphthylamine (**9**) the reaction lost its regioselectivity and yields a mixture of the monobrominated products, 4-bromo-1-naphthylamine (**25a**) and 2-bromo-1-naphthylamine (**25b**), in ca. 1:1 ratio (HPLC).

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The use of K_2CO_3 at 60 °C yields the dibrominated products, 2,4-dibromo-1-naphthol (**32**) and 2,4-dibromo-1-naphthylamine (**33**), respectively. All the prepared derivatives and yields are summarized in Tables 1 and 2. The isolated yields are generally somewhat lower due to the losses during preparative HPLC purification caused mostly by partial irreversible binding of the phenolic products to the column matrix.

A major advantage of the method is the high regioselectivity of flavonoid monobromination. Somehow lower yields and complicated removal of cinnamic acid from simple aromatic products are disadvantages of this method.

In conclusion, we developed a mild and regioselective bromination method for the bromination of flavonoids and simple aromatic compounds. Using this method, we prepared monobrominated and dibrominated derivatives of silymarin flavonolignans and other flavonoids. These bromo derivatives can be used for the preparation of flavonolignan dimers connected via the A-ring using the Suzuki cross-coupling reaction.

EXPERIMENTAL SECTION

General Experimental Procedures. Procedures using oxygen- and/or moisture-sensitive materials were handled with anhydrous solvents (*vide infra*) under an atmosphere of dry argon. Heating was performed using heating blocks. Analytical TLC was performed on Al plates (silica gel 60 F_{254}; Merck, Darmstadt, Germany) and visualized using UV light (254 nm).

Purification was performed in a preparative HPLC system using an ASAHIPAK GS-310 20F column (Shodex, Munich, Germany), with MeOH as the mobile phase, flow rate 5 mL/min, and detection at 254 and 369 nm. The preparative HPLC (Shimadzu, Kyoto, Japan) system consisted of an LC-8A high-pressure pump with an SPD-20A dual-wavelength detector (with preparative cell), FRC-10A, and fraction collector. The system was connected to a PC using a CBM-20A command module and controlled by the LabSolution 1.24 SPI software suite supplied with the instrument.

All analytical HPLC separations were performed with a Shimadzu Prominence System (Shimadzu, Kyoto, Japan), consisting of a DGU-20A mobile phase degasser, two LC-20AD high-pressure pumps, a SIL-20AC cooling autosampler, a CTO-10AS column oven, and an SPDM20 A diode array detector. Shimadzu Solution software was used for the collection of chromatographic data at a rate of 40 Hz. A Chromolith Performance RP-18e monolithic column (100 × 3 mm i.d., Merck, Darmstadt, Germany) coupled with a guard column (5 × 4.6 mm, Merck, Darmstadt, Germany) was used. Mobile phase A, $CH_3CN/H_2O/HCO_2H$ (5:95:0.1), and phase B, $CH_3CN/H_2O/HCO_2H$ (80:20:0.1), were employed in the analyses, with the following gradient: 0−6 min 10−80% B; 6−8 min 80% B; 10−12 min 80−10% A. The flow rate was 0.4 mL/min at 25 °C. MS parameters were as follows: negative mode; ESI interface voltage, 4.5 kV; detector voltage, 1.15 kV; nebulizing gas flow, 1.5 mL/min; drying gas flow, 15 mL/min; heat block temperature, 200 °C; DL temperature, 250 °C; scan mode 300−800 *m/z*. The PDA data were acquired in the 200−450 nm range, and the signal at 285 nm was used for monitoring the separation. Flash column chromatography was performed on Kieselgel 60 (60−200 mesh). MPLC was carried out on a Biotage Selekt flash purification system. Separations were performed on a Biotage Sfär C18 D-Duo 100 Å 30 μm (6 g) column.

The NMR analyses were carried out on Bruker Avance III 700 MHz (700.13 MHz for ^1H, 176.05 MHz for ^{13}C), Bruker Avance III 600 MHz (600.23 MHz for ^1H, 150.93 MHz for ^{13}C), and Bruker Avance III 400 MHz (399.87 MHz for ^1H, 100.55 MHz for ^{13}C) spectrometers in DMSO-d_6 at 30 °C and in $CDCl_3$ at 20 °C. The signals in DMSO-d_6 and $CDCl_3$ were used as references (δ_H 2.499, δ_C 39.46 for DMSO-d_6 and δ_H 7.263, δ_C 77.01 for $CDCl_3$). For structure elucidation the following NMR experiments were used: ^1H NMR, ^{13}C NMR, *J*-resolved, COSY, $^1H-^{13}C$ HSQC, $^1H-^{13}C$ HMBC, ROESY, band-selective $^1H-^{13}C$ HSQC, band-selective $^1H-^{13}C$ HMBC, $^1H-^{15}N$ HMBC, and 1D TOCSY. The spectra were acquired using the manufacturer's software. ^1H and ^{13}C NMR spectra were zero filled to 4-fold data points and multiplied by window function before Fourier transformation. A two-parameter double-exponential Lorentz-Gauss function was applied for ^1H to improve resolution, and line broadening (1 Hz) was applied to get a better ^{13}C signal-to-noise ratio. Chemical shifts are given on the δ-scale with digital resolution justifying the reported values to three (δ_H) or two (δ_C) decimal places.

Commercially available reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA), Alfa Aesar (Haverhill, MA, USA), Acros Organics (Morris Plains, NJ, USA), and TCI Chemicals (Tokyo, Japan) and, unless otherwise stated, were used without further purification. Pure diastereomers of silybin were prepared using diastereomeric enzymatic resolution.[27] 2,3-Dehydrosilybin AB (**5**) and 2,3-dehydrosilychristin A (**7**) were prepared as described previously.[28,29] Alkylated derivatives of quercetin were prepared as described previously.[14] Selectively alkylated derivatives of silybin were prepared as described previously.[30]

General Method A for Monobromination. α,β-Dibromohydrocinnamic acid (3.0 equiv) and Cs_2CO_3 (0.5 equiv) were added to a solution of starting material (1.0 equiv) in dry DMF at room temperature. The reaction mixture was heated and stirred at 40 °C for 16 h. The reaction mixture was poured into water and extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (3 × 10 mL), dried over Na_2SO_4, and evaporated *in vacuo*. Unless stated otherwise the residue was purified by HPLC preparative chromatography (ASAHIPAK, MeOH 5 mL/min isocratic), yielding the corresponding product.

*6-Bromotaxifolin (**17**).* General method A was followed and yielded **17** as a yellow solid (50 mg, 40%): HRMS (ESI, *m/z*) calcd for $C_{15}H_{10}O_7{}^{79}Br$ $[M - H]^-$ 380.96154, found 380.96121; HRMS (ESI, *m/z*) calcd for $C_{15}H_{10}O_7{}^{81}Br$ $[M - H]^-$ 382.96154, measured 382.95898.

*8-Bromoquercetin (**18**).* General method A was followed and yielded **18** as a yellow solid (30 mg, 25%): HRMS (ESI, *m/z*) calcd for $C_{15}H_8O_7{}^{79}Br$ $[M - H]^-$ 378.94589, found 378.94530; HRMS (ESI, *m/z*) calcd for $C_{15}H_8O_7{}^{81}Br$ $[M - H]^-$ 380.94589, measured 380.94319.

*8-Bromomyricetin (**19**).* General method A was followed and yielded **19** as a yellow solid (60 mg, 49%): HRMS (ESI, *m/z*) calcd for $C_{15}H_9O_8{}^{79}Br$ $[M - H]^-$ 394.94080, found 394.94014; HRMS (ESI, *m/z*) calcd for $C_{15}H_9O_8{}^{81}Br$ $[M - H]^-$ 396.94080, measured 396.93805.

*6-Bromosilybin (**20**).* α,β-Dibromohydrocinnamic acid (924 mg, 3.0 equiv, 3 mmol) and Cs_2CO_3 (162.5 mg, 0.5 equiv, 0.5 mmol) were added to a solution of silybin (mixture of diastereomers A and B in 1:1 ratio) (482 mg, 1.0 equiv, 1 mmol) in 15 mL of dry DMF at room temperature. The reaction mixture was heated to 40 °C and stirred for 16 h. The reaction mixture was poured into water and extracted with EtOAc (3 × 30 mL). Combined organic fractions were washed with brine (2 × 30 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by HPLC preparative chromatography (ASAHIPAK, MeOH 5 mL/min isocratic), yielding **20** as a yellow oil (200 mg, 36%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{79}Br$ $[M - H]^-$ 559.02453, found 559.02463; HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{81}Br$ $[M - H]^-$ 561.02453, measured 561.02256.

*6-Bromosilybin A (**20a**).* General method A was followed and yielded **20a** as a yellow solid (35 mg, 30%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{79}Br$ $[M - H]^-$:559.02453, found 559.02374; HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{81}Br$ $[M - H]^-$ 561.02453, found 561.02155.

*6-Bromosilybin B (**20b**).* General method A was followed and yielded **20b** as a yellow solid (40 mg, 35%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{79}Br$ $[M - H]^-$ 559.02453, found 559.02423; HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{81}Br$ $[M - H]^-$ 561.02453, found 561.02181.

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*8-Bromodehydrosilybin (**21**).* General method A was followed and yielded **21** as a yellow solid (35 mg, 30%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{18}O_{10}{}^{79}Br$ $[M - H]^-$ 557.00888, found 557.00790; HRMS (ESI, *m/z*) calcd for $C_{25}H_{18}O_{10}{}^{81}Br$ $[M - H]^-$ 559.00888, found 559.00566.

*6-Bromosilychristin A (**22**).* General method A was followed and yielded **22** as a yellow solid (127 mg, 55%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{79}Br$ $[M - H]^-$ 559.02453, found 559.02367; HRMS (ESI, *m/z*) calcd for $C_{25}H_{20}O_{10}{}^{81}Br$ $[M - H]^-$ 561.02453, found 561.02144.

*8-Bromodehydrosilychristin (**23**).* General method A was followed and yielded **23** as a yellow solid (20 mg, 20%). The product was contaminated with aliphatic impurities (Figure S17, Supporting Information). Due to the paucity of the starting material, the reaction could not be repeated. HRMS (ESI, *m/z*) calcd for $C_{25}H_{18}O_{10}{}^{79}Br$ $[M - H]^-$ 557.00888, found 557.00812; HRMS (ESI, *m/z*) calcd for $C_{25}H_{18}O_{10}{}^{81}Br$ $[M - H]^-$ 559.00888, found 559.00598.

*2-Bromo-1-naphthol (**24**).* General method A was followed. The residue was purified by FCC (cyclohexane/EtOAc, 40:1) and afforded **24** as a white solid (65 mg, 46%); HRMS (ESI, *m/z*) calcd for $C_{10}H_7O^{79}Br$ $[M - H]^-$ 220.96075, found: 220.96083; HRMS (ESI, *m/z*) calcd for $C_{10}H_7O^{81}Br$ $[M - H]^-$ 222.96075, found 222.95870.

*4-Bromo-1-naphthylamine (**25a**) and 2-Bromo-1-naphthylamine (**25b**).* General method A was followed and afforded **25** (46 mg, 44%, isolated as a inseparable mixture of 2- and 4-bromo-1-naphthylamine): HRMS (ESI, *m/z*) calcd for $C_{10}H_9{}^{79}BrN$ $[M + H]^+$ 221.99129, found 221.99114; HRMS (ESI, *m/z*) calcd for $C_{10}H_9{}^{81}BrN$ $[M + H]^+$ 223.99129, found 223.98899.

*8-Bromo-3,7-dihydroxyflavone (**26**).* General method A was followed and afforded **26** as a white solid (43 mg, 40%): HRMS (ESI, *m/z*) calcd for $C_{15}H_{10}O_4{}^{79}Br$ $[M + H]^+$ 332.97570, found: 332.97586; HRMS (ESI, *m/z*) calcd for $C_{15}H_{10}O_4{}^{79}Br$ $[M + H]^+$ 334.97570, found 334. 97381.

*8-Bromo-3,3′,4′,7-tetra-O-methylquercetin (**34a**) and 6-Bromo-3,3′,4′,7-tetra-O-methylquercetin (**34b**).* General method A was followed and afforded a mixture of **34a** and **34b**, ca. 1:1 (HPLC), as a yellow solid (50 mg, 43%): HRMS (ESI, *m/z*) calcd for $C_{19}H_{18}O_7{}^{79}Br$ $[M + H]^+$ 437.02304, found 437.02312; HRMS (ESI, *m/z*) calcd for $C_{19}H_{18}O_7{}^{81}Br$ $[M + H]^+$ 439.02304, found 439.02115.

*8-Bromo-3,3′,4′,5,7-penta-O-methylquercetin (**35**).* General method A was followed and afforded **35** as yellow solid (50 mg, 41%): HRMS (ESI, *m/z*) calcd for $C_{20}H_{20}O_7{}^{79}Br$ $[M + H]^+$ 451.03869, found 451.03876; HRMS (ESI, *m/z*) calcd for $C_{20}H_{20}O_7{}^{81}Br$ $[M + H]^+$ 453.03869, found 453.03676.

*8-Bromo-3,3′,4′,7-tetra-O-isopropylquercetin (**36a**) and 6-Bromo-3,3′,4′,7-tetra-O-isopropylquercetin (**36b**).* General method A was followed. The residue was purified by the flash purification system and afforded **36a** as yellow oil (36 mg, 25%) and **36b** as a yellow oil (45 mg, 32%): HRMS (ESI, *m/z*) calcd for $C_{27}H_{34}O_7{}^{79}Br$ $[M + H]^+$ 549.14824, found 549.1483; HRMS (ESI, *m/z*) calcd for $C_{27}H_{34}O_7{}^{81}Br$ $[M + H]^+$ 551.14824, found 551.14647.

*8-Bromo-3,3′,4′,5,7-isopropyl-O-methylquercetin (**37**).* General method A was followed. The residue was purified by FCC (petroleum ether/EtOAc, 6:1) and afforded **37** as a white solid (45 mg, 40%): HRMS (ESI, *m/z*) calcd for $C_{30}H_{40}O_7{}^{79}Br$ $[M + H]^+$ 591.19519, found 591.19545; HRMS (ESI, *m/z*) calcd for $C_{30}H_{40}O_7{}^{81}Br$ $[M + H]^+$ 593.19519, found 593.19351.

*6-Bromo-7-O-methylsilybin (**38**).* General method A was followed and afforded **39** as a white solid (31 mg, 30%, containing 20% of the 8-bromo derivative): HRMS (ESI, *m/z*) calcd for $C_{26}H_{22}O_{10}{}^{79}Br$ $[M - H]^-$ 573.04018, found 573.04049; HRMS (ESI, *m/z*) calcd for $C_{26}H_{22}O_{10}{}^{81}Br$ $[M - H]^-$575.04018, measured 573.03866.

*6-Bromo-7-O-benzylsilybin (**39**).* General method A was followed and afforded **39** as a white solid (50 mg, 44%, containing 20% of the 8-bromo derivative): HRMS (ESI, *m/z*) calcd for $C_{32}H_{26}O_{10}{}^{79}Br$ $[M - H]^-$ 649.07148, found 649.07055; HRMS (ESI, *m/z*) calcd for $C_{32}H_{26}O_{10}{}^{79}Br$ $[M - H]^-$651.07148, found 649.06724.

General Method B for Dibromination. α,β-Dibromohydrocinnamic acid (3.0 equiv) and K_2CO_3 (0.5 equiv) were added to a solution of starting material (1.0 equiv) in dry DMF at room temperature. The reaction mixture was heated and stirred at 60 °C for 16 h. The reaction mixture was poured into water and extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Unless otherwise stated the residue was purified by HPLC preparative chromatography (ASAHIPAK, 5 mL/min isocratic) to give the corresponding product.

*6,8-Dibromotaxifolin (**27**).* General procedure B was used and afforded **27** as a yellow solid (70 mg, 46%): HRMS (ESI, *m/z*) calcd for $C_{15}H_8O_7{}^{79}Br_2$ $[M - H]^-$ 458.87205, found 458.87161; HRMS (ESI, *m/z*) calcd for $C_{15}H_8O_7{}^{81}Br_2$ $[M - H]^-$ 461.87205, found 462.86710.

*6,8-Dibromoquercetin (**28**).* General procedure B was followed and afforded **28** as a yellow solid (75 mg, 50%): HRMS (ESI, *m/z*) calcd for $C_{15}H_6O_7{}^{79}Br_2$ $[M - H]^-$ 456.85640, found 456.85593; HRMS (ESI, *m/z*) calcd for $C_{15}H_6O_7{}^{81}Br_2$ $[M - H]^-$ 460.85640, found 460.85141.

*6,8-Dibromosilybin (**29**).* α,β-Dibromohydrocinnamic acid (924 mg, 3.0 equiv, 3 mmol) and K_2CO_3 (69 mg, 0.5 equiv, 0.5 mmol) were added to a solution of silybin (**4**) (an equimolar mixture of silybin diastereomers A and B) (482 mg, 1.0 equiv, 1 mmol) in 15 mL of dry DMF at room temperature. The reaction mixture was heated and stirred at 60 °C for 16 h. The reaction mixture was poured into water and extracted with EtOAc (3 × 30 mL). The combined organic fractions were washed with brine (3 × 30 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by HPLC preparative chromatography (ASAHIPAK, MeOH 5 mL/min isocratic) to give **29** as a yellow oil (302 mg, 47%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{79}Br_2$ $[M - H]^-$ 636.93505, found 636.93513; HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{81}Br_2$ $[M - H]^-$ 640.93505, found 640.93079.

*6,8-Dibromosilybin A (**29a**).* General procedure B was used and afforded **29a** as a yellow solid (55 mg, 42%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{79}Br_2$ $[M - H]^-$ 636.93505, found 636.93445; HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{81}Br_2$ $[M - H]^-$ 640.93505, found 640.92999.

*6,8-Dibromosilybin B (**29b**).* General procedure B was followed and afforded **29b** as a yellow solid (165 mg, 42%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{79}Br_2$ $[M - H]^-$ 636.93505, found 636.93445; HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{81}Br_2$ $[M - H]^-$ 640.93505, found 640.92986.

*6,8-Dibromodehydrosilybin (**30**).* General procedure B was followed and afforded **30** as a yellow solid (40 mg, 30%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{17}O_{10}{}^{79}Br_2$ $[M - H]^-$ 634.91940, found 634.91859; HRMS (ESI, *m/z*) calcd for $C_{25}H_{17}O_{10}{}^{81}Br_2$ $[M - H]^-$ 638.91940, found 638.91461.

*6,8-Dibromosilychristin A (**31**).* General procedure B was employed and afforded **31** as a yellow solid (57 mg, 43%): HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{79}Br_2$ $[M - H]^-$ 636.93505, found 636.93457; HRMS (ESI, *m/z*) calcd for $C_{25}H_{19}O_{10}{}^{79}Br_2$ $[M - H]^-$ 640.93505, found 640.93030.

*2,4-Dibromo-1-naphthol (**32**).* General procedure B was employed and afforded **32** as a yellow solid (85 mg, 41%): HRMS (ESI, *m/z*) calcd for $C_{10}H_6{}^{79}Br_2O$ $[M - H]^-$ 298.87126, found 298.87132; HRMS (ESI, *m/z*) calcd for $C_{10}H_6{}^{81}Br_2O$ $[M - H]^-$ 302.87126, found 302.86699.

*2,4-Dibromo-1-naphthylamine (**33**).* General procedure B was followed and afforded **33** as a yellow solid (92 mg, 44%): HRMS (ESI, *m/z*) calcd for $C_{10}H_8{}^{79}Br_2N$ $[M + H]^+$ 299.90180, found 299.90140; HRMS (ESI, *m/z*) calcd for $C_{10}H_8{}^{81}Br_2N$ $[M + H]^+$ 299.90180, found 299.89685.

*6,8-Dibromo-3,3′,4′,7-tetra-O-isopropylquercetin (**40**).* General method B was followed. The residue was purified by FCC (6:1 petroleum ether/EtOAc) and afforded **40** as a white solid (70 mg, 46%): HRMS (ESI, *m/z*) calcd for for $C_{27}H_{33}O_7{}^{79}Br_2$ $[M + H]^+$ 627.05875, found 627.05914. $C_{27}H_{33}O_7{}^{81}Br_2$ $[M + H]^+$ 631.05875, found 631.05475.

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■ ASSOCIATED CONTENT

Supporting Information

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Spectroscopic data of the new compounds, including the NMR spectra and data, HPLC-MS, and HRMS analyses (PDF)

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Notes

The authors declare no competing financial interest.

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